

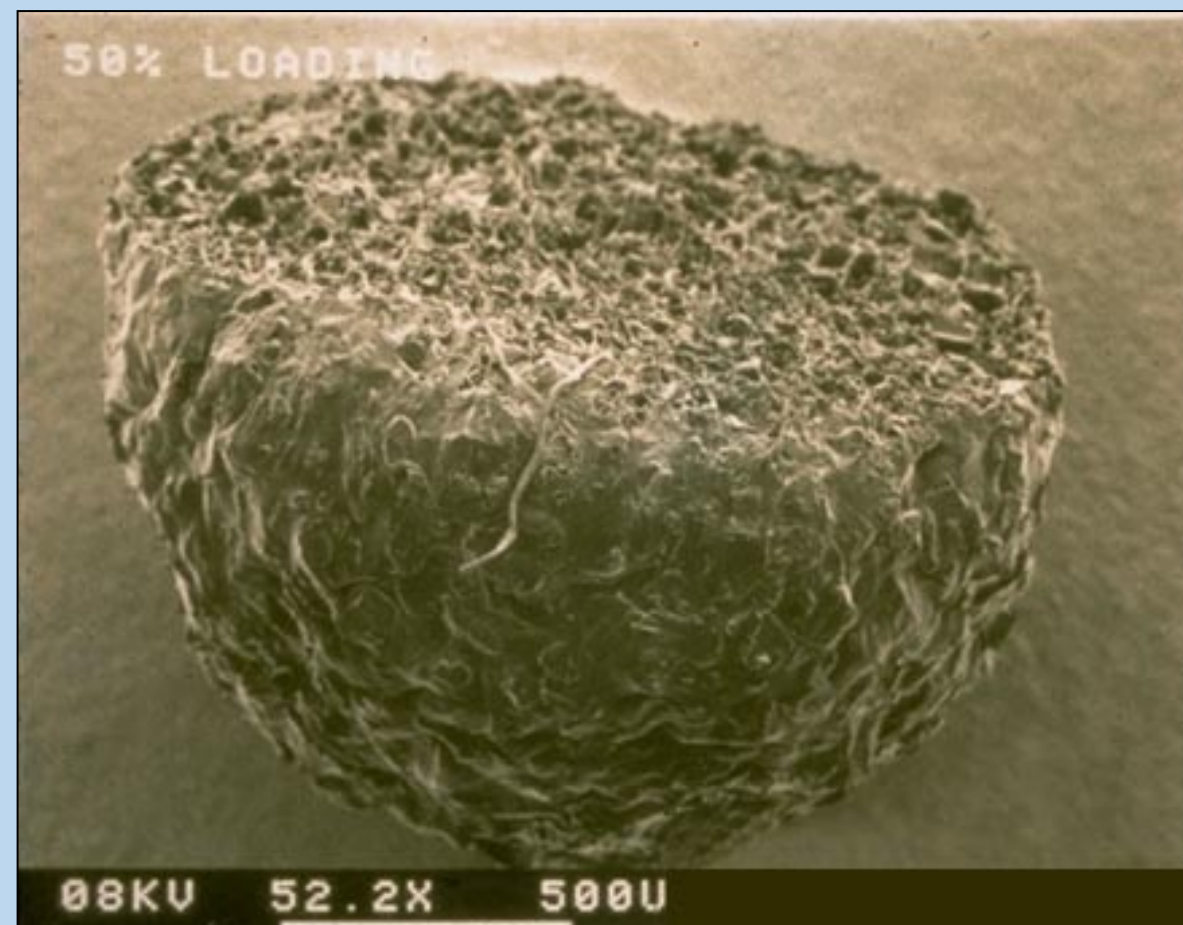
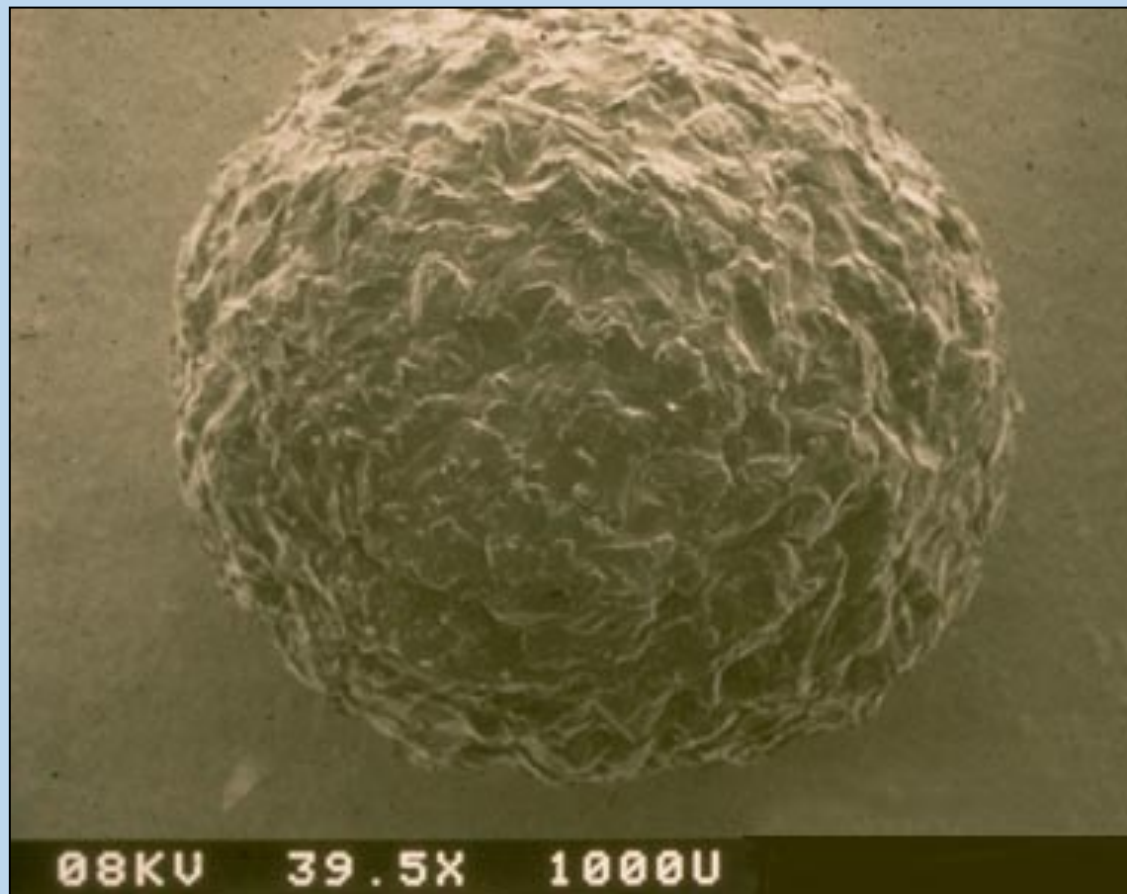
# ***ADVANCES IN DRUG DELIVERY***

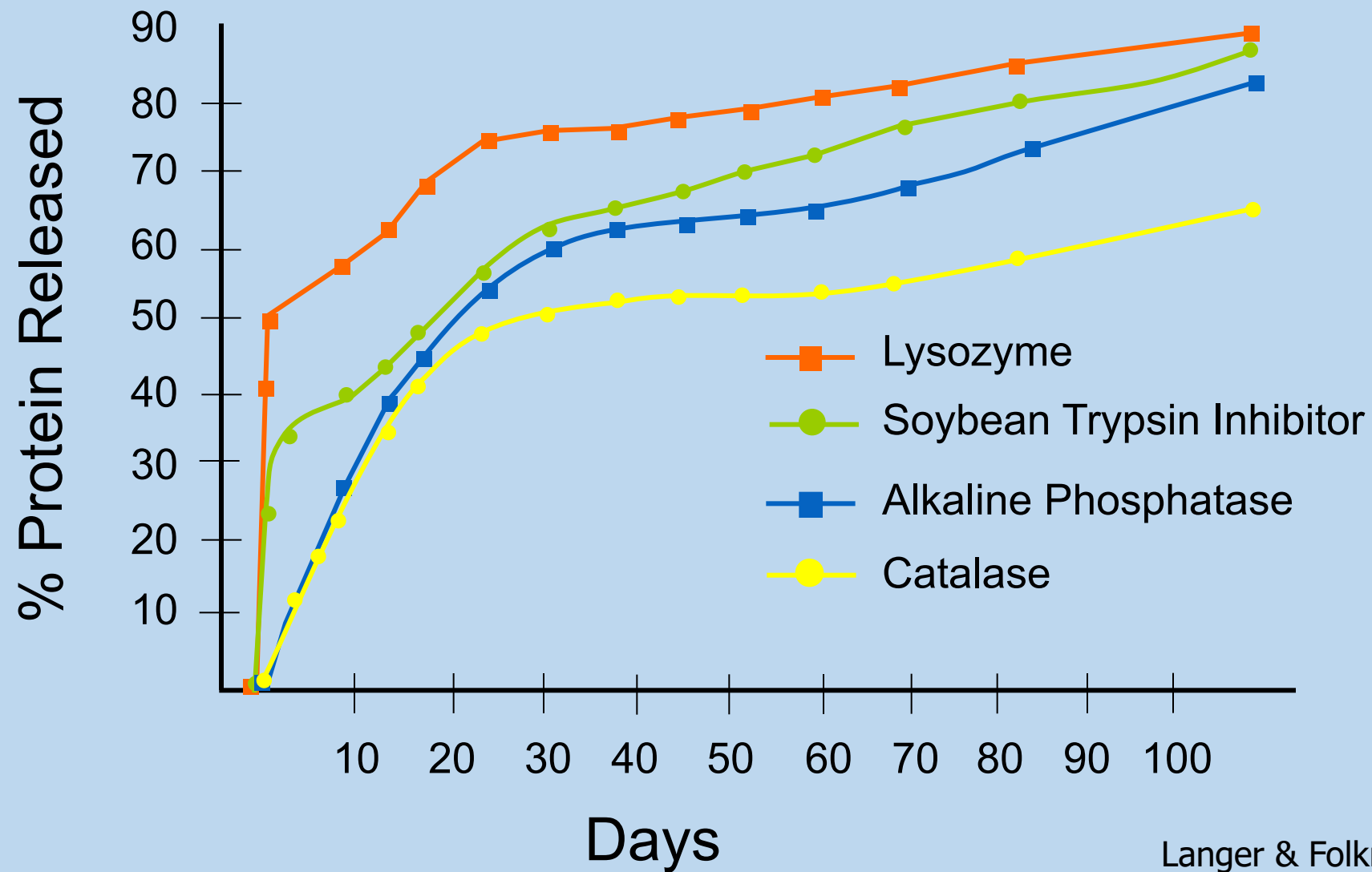
9 June 2021

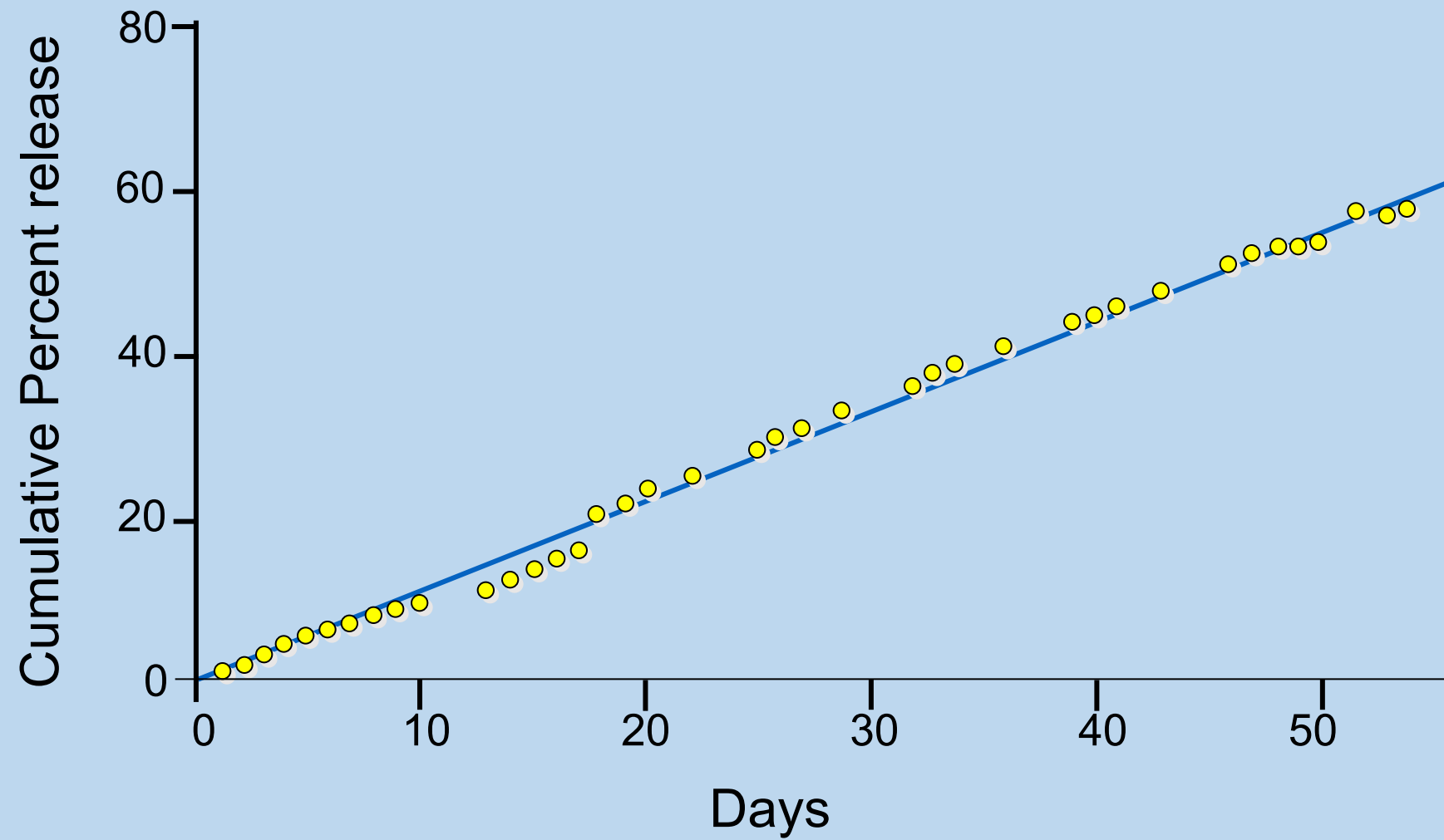
Dr. Robert Langer, Sc.D.

Institute Professor

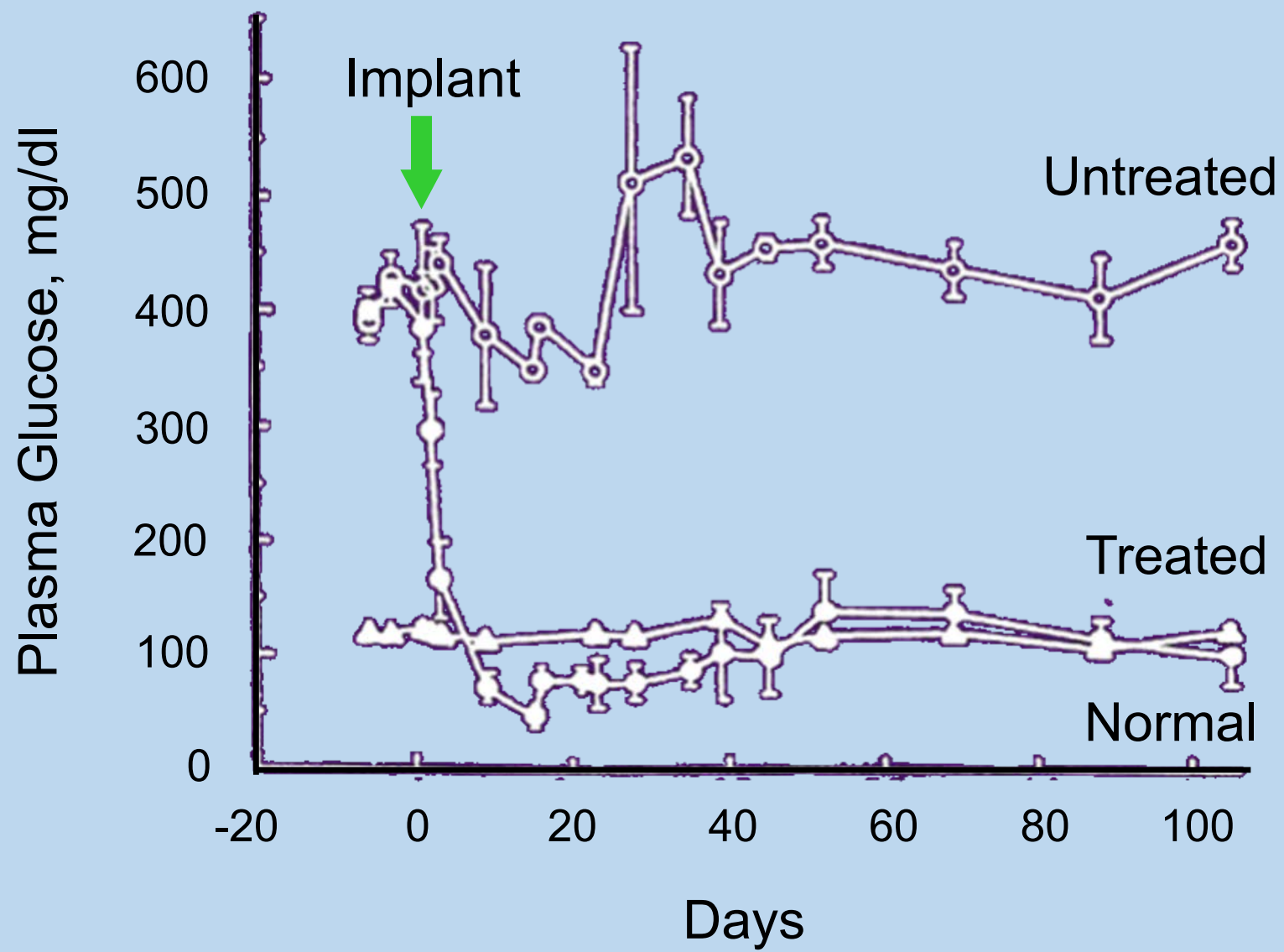
Massachusetts Institute of Technology





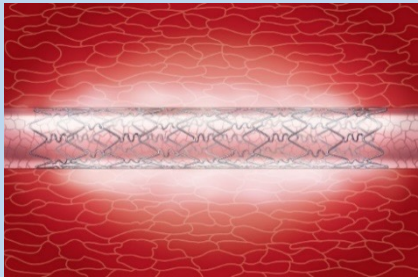
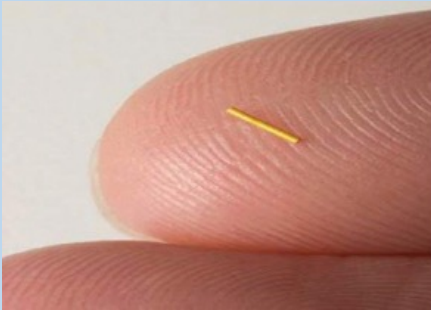
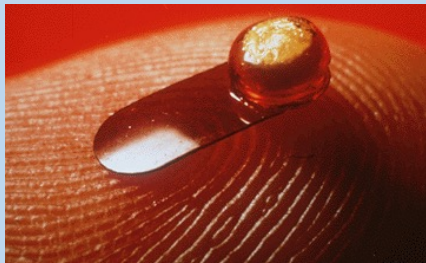
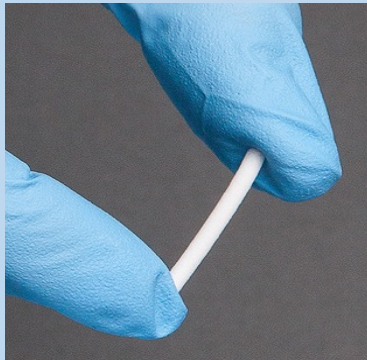


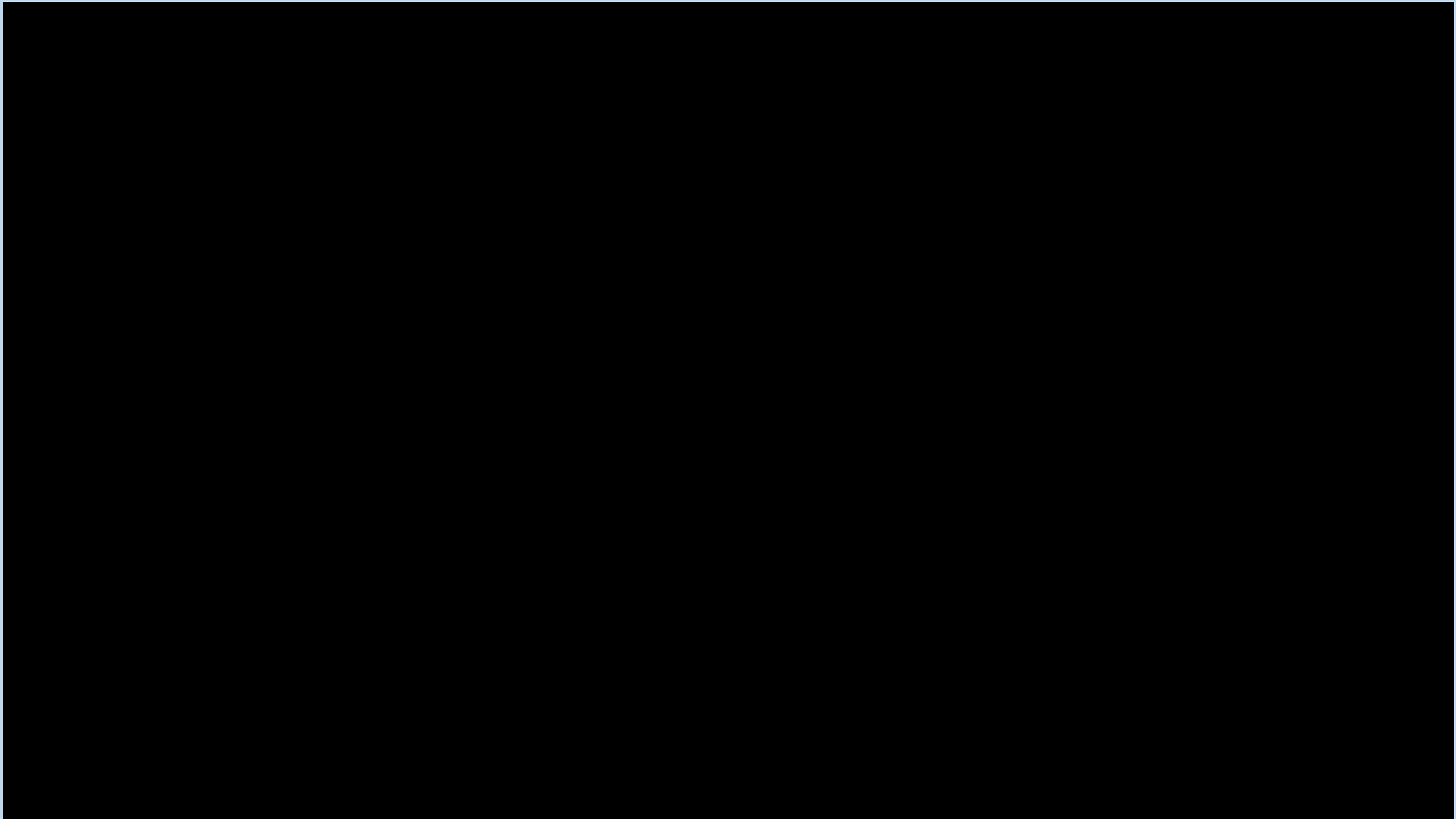




“Generally the agent to be released is a relatively small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g. proteins, could be released by such a technique because of their extremely small permeation rates... However, Folkman and Langer have reported some surprising results that clearly demonstrate the opposite.”

-Stannett, Koros, Paul, Baker, Lonsdale, *Adv. Poly. Sci.*, 1979.





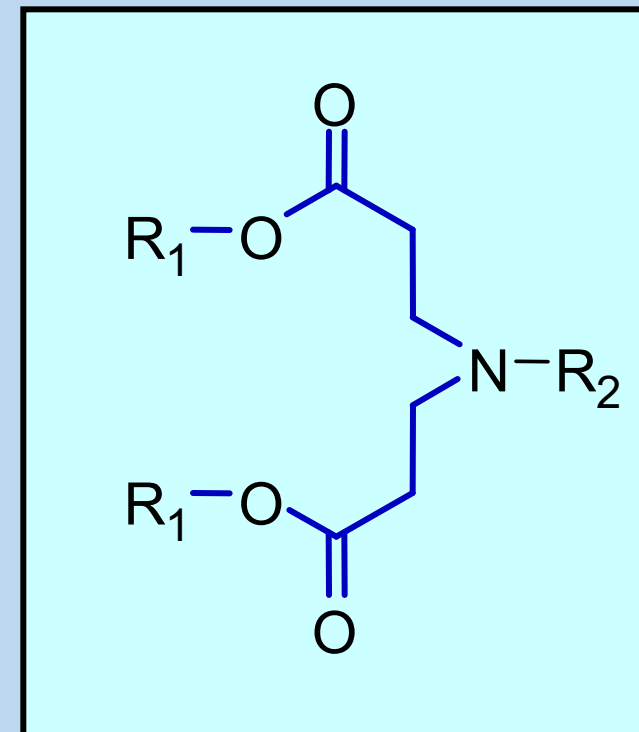
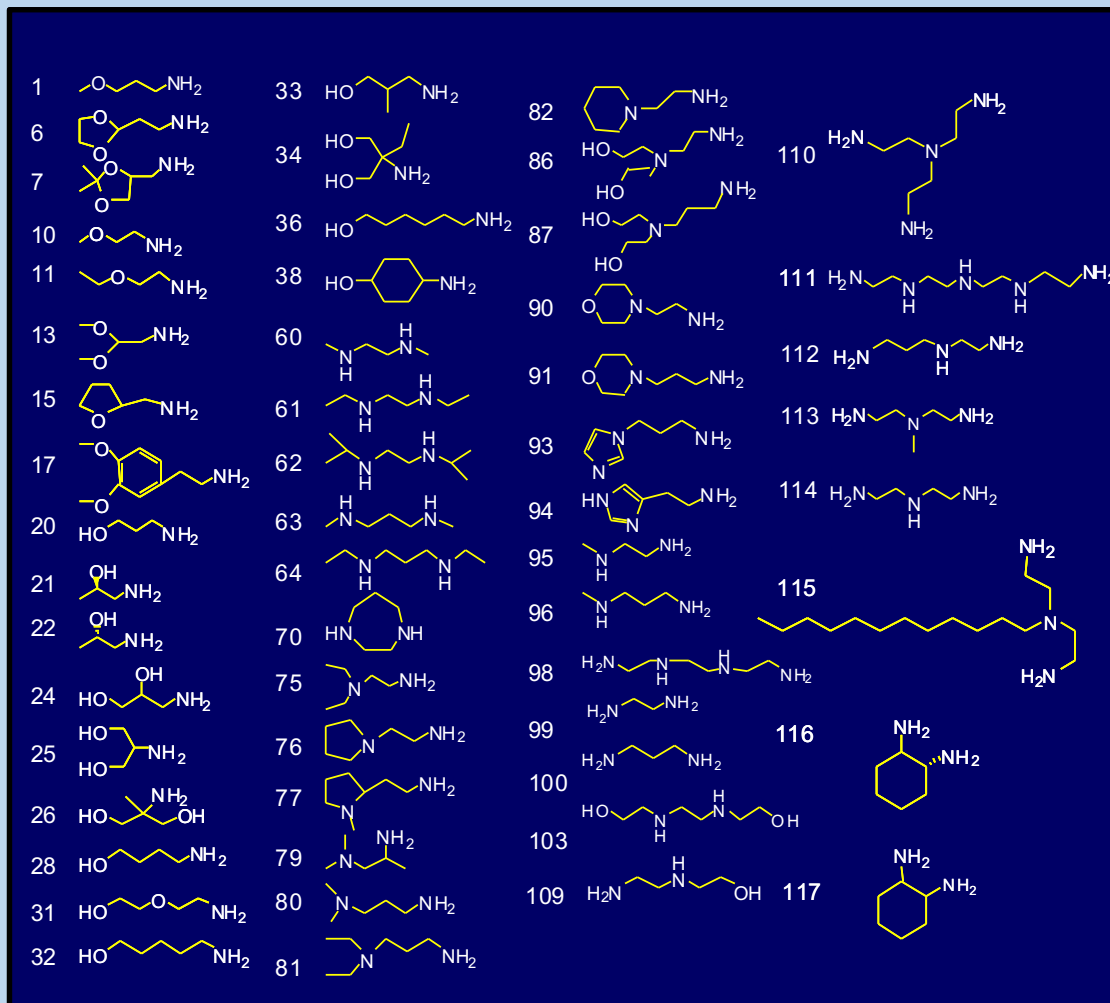
Small molecules

Genetic therapy (e.g., siRNA, mRNA)

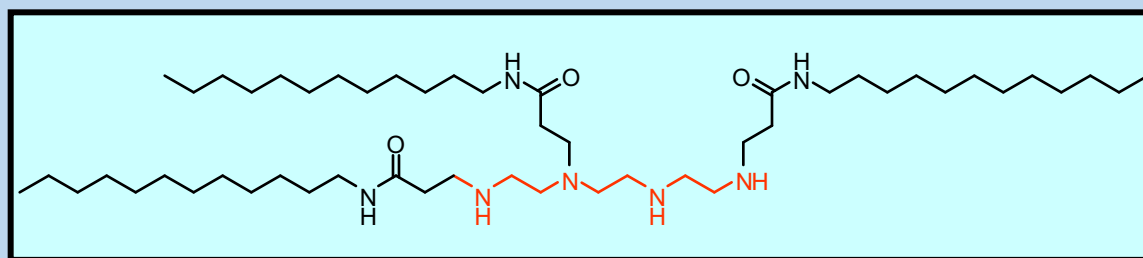
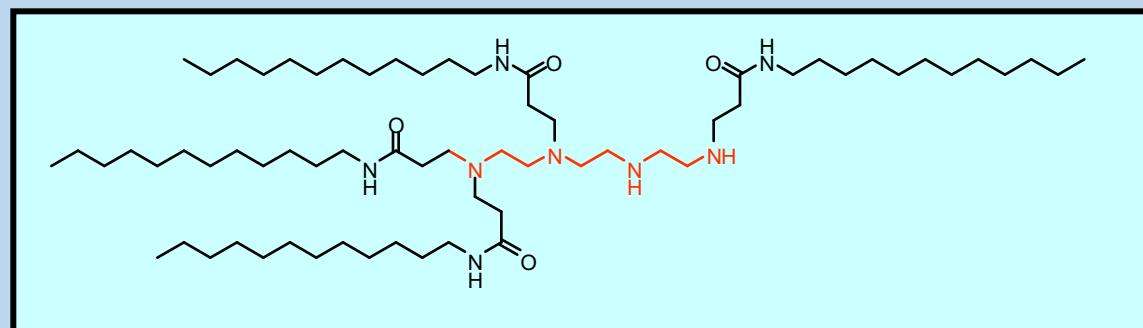
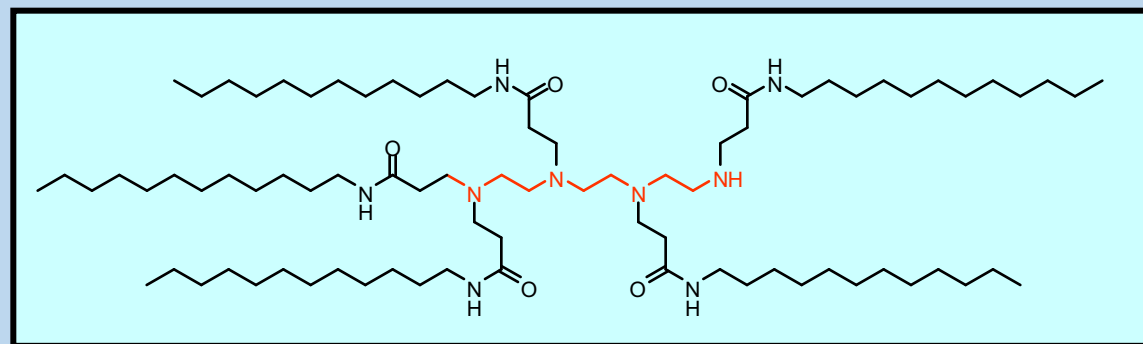
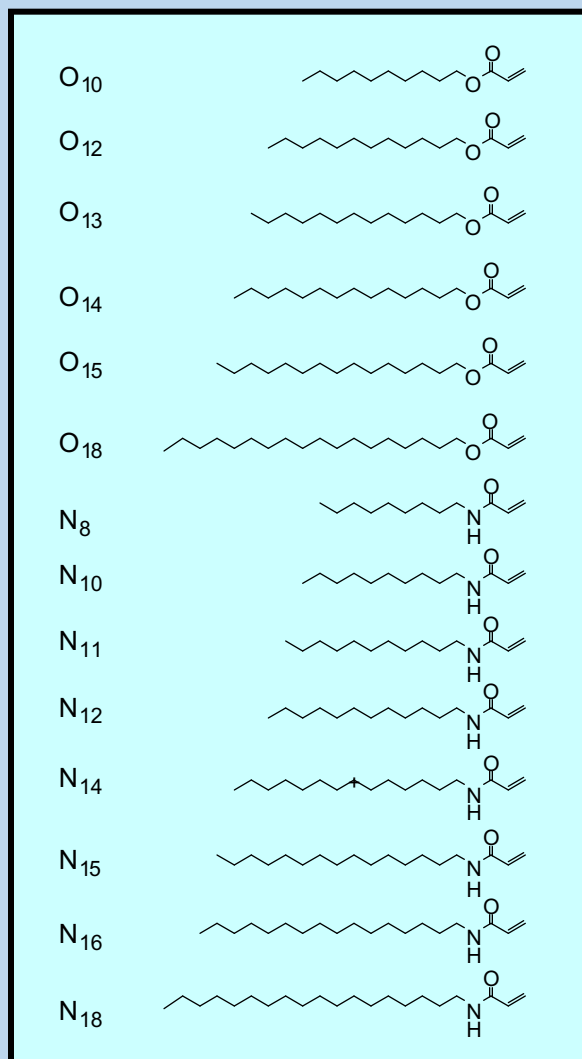
# *Combinatorial lipid synthesis wish list*

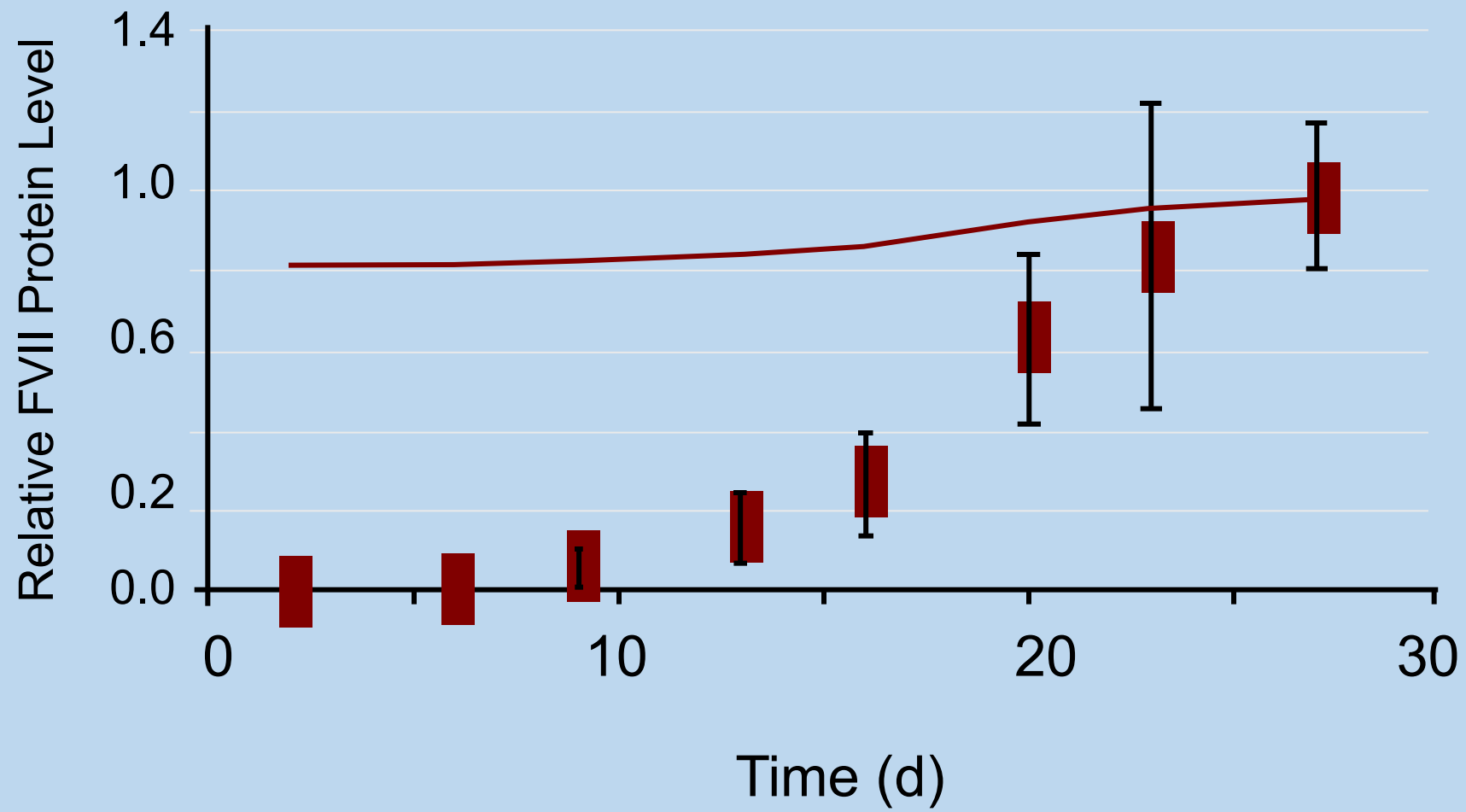
- One protocol for high-throughput, parallel synthesis
- Generation of a chemically diverse library
- As few steps as possible
- No protection/deprotection
- No catalysts
- No solvent switches, preferably no solvent
- No purification
- Amenable to Parallel Formulation

# Large variation in R group

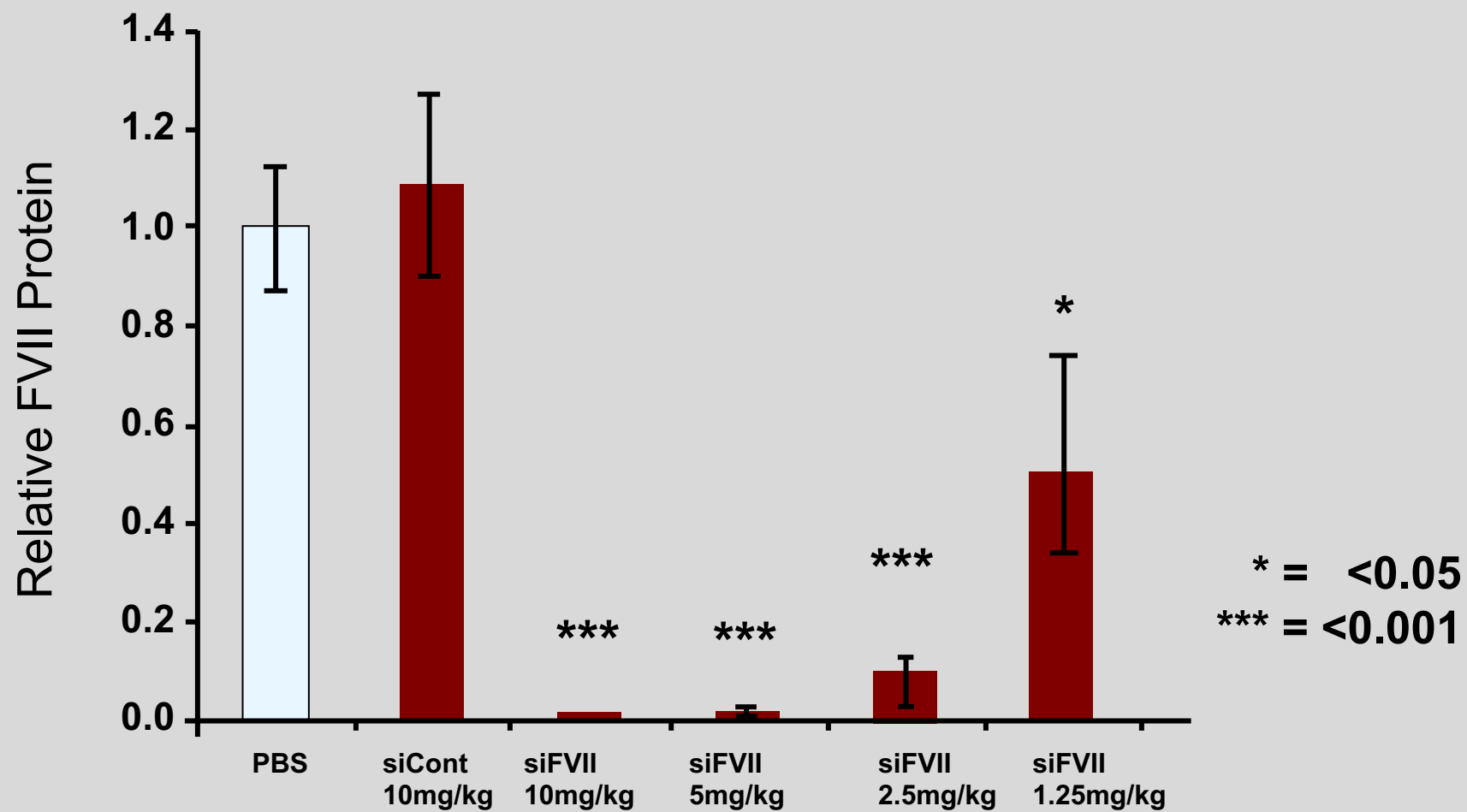


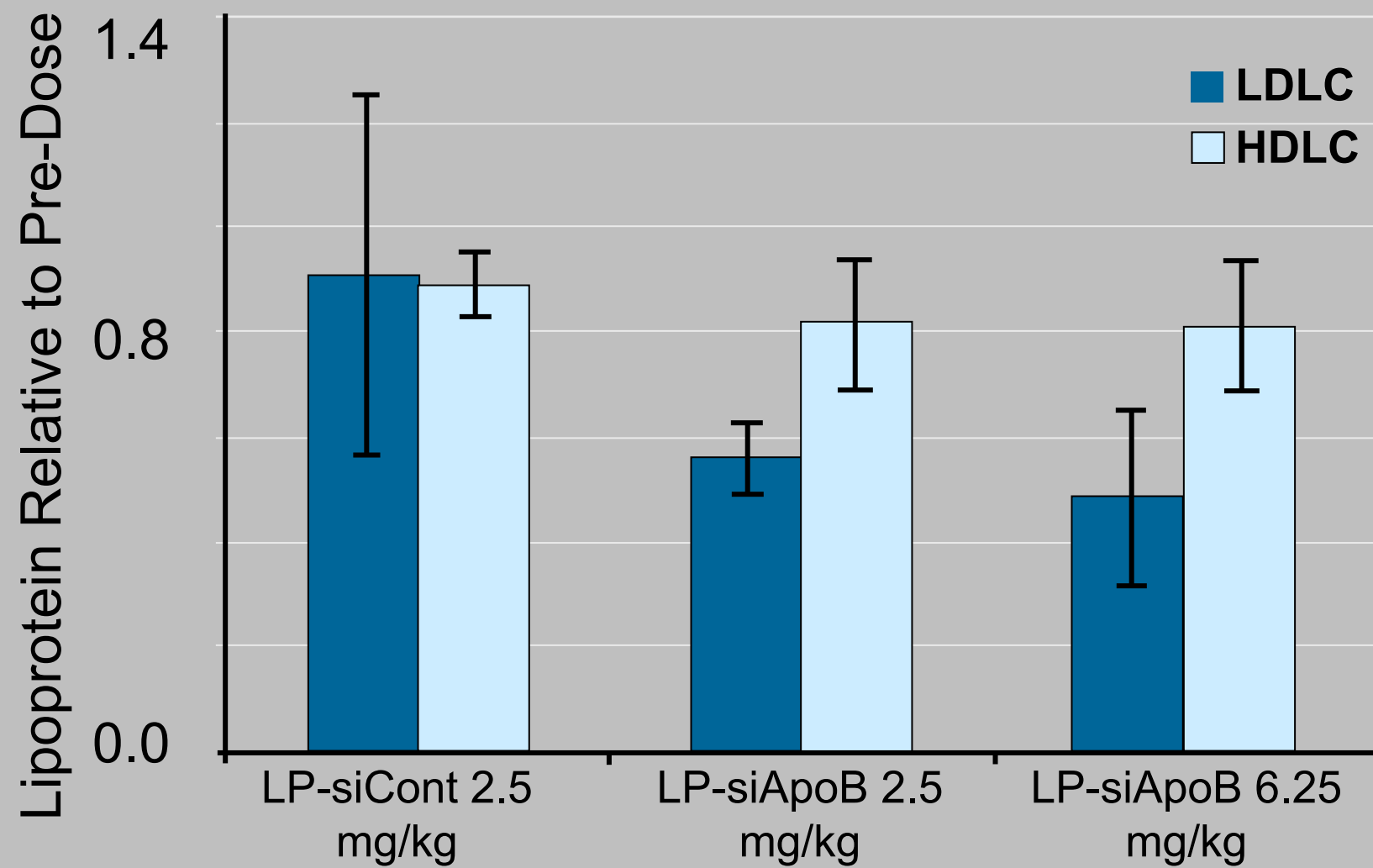
# Variable tail length and number of tails



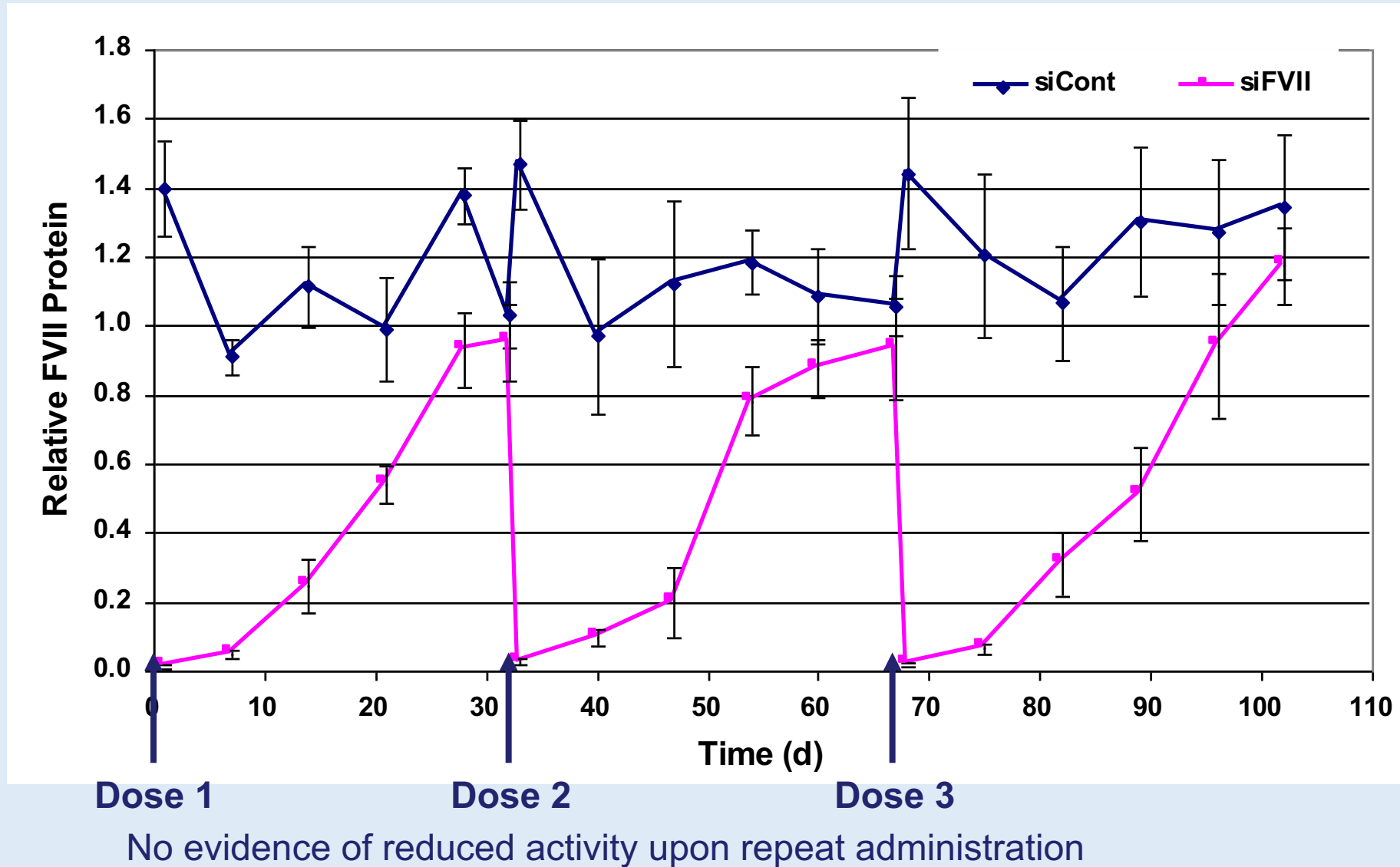




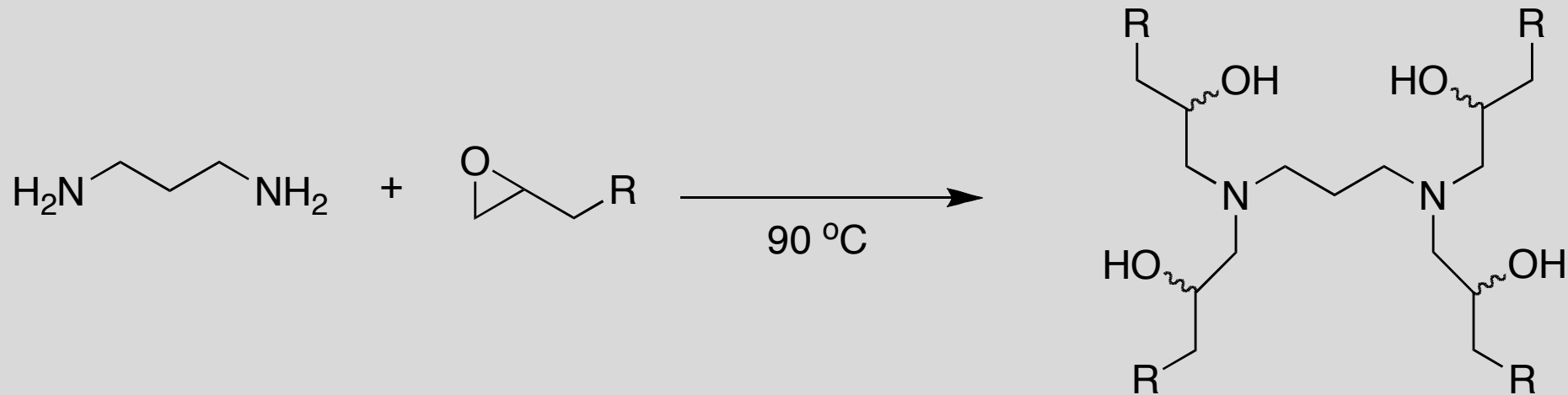




# *Fully reversible, specific liver knockdown*



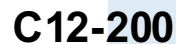
# Improved lipidoid libraries



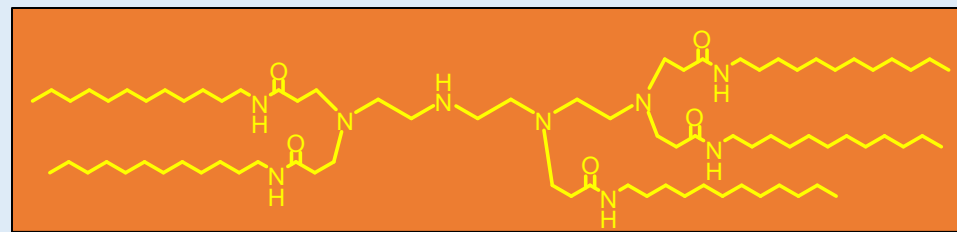
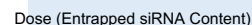
Created library of 150 new compounds

- 10 different commercially available epoxide-terminated tails
- Selection of amines from original lipidoid library with bias towards good performing amines from previous libraries
- Tested *FIRST IN VITRO*

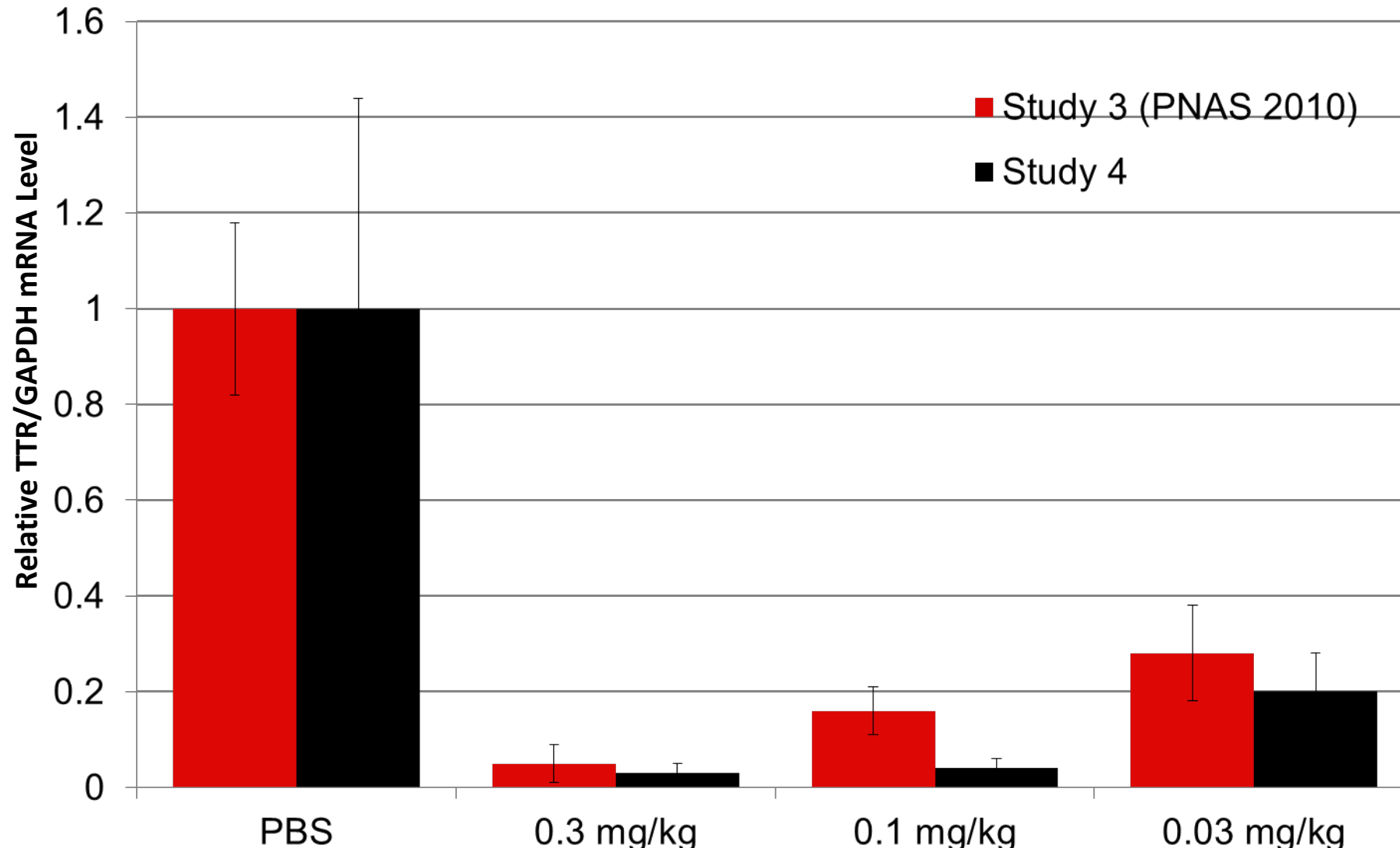
## Relative FVII Expression



# LNP01

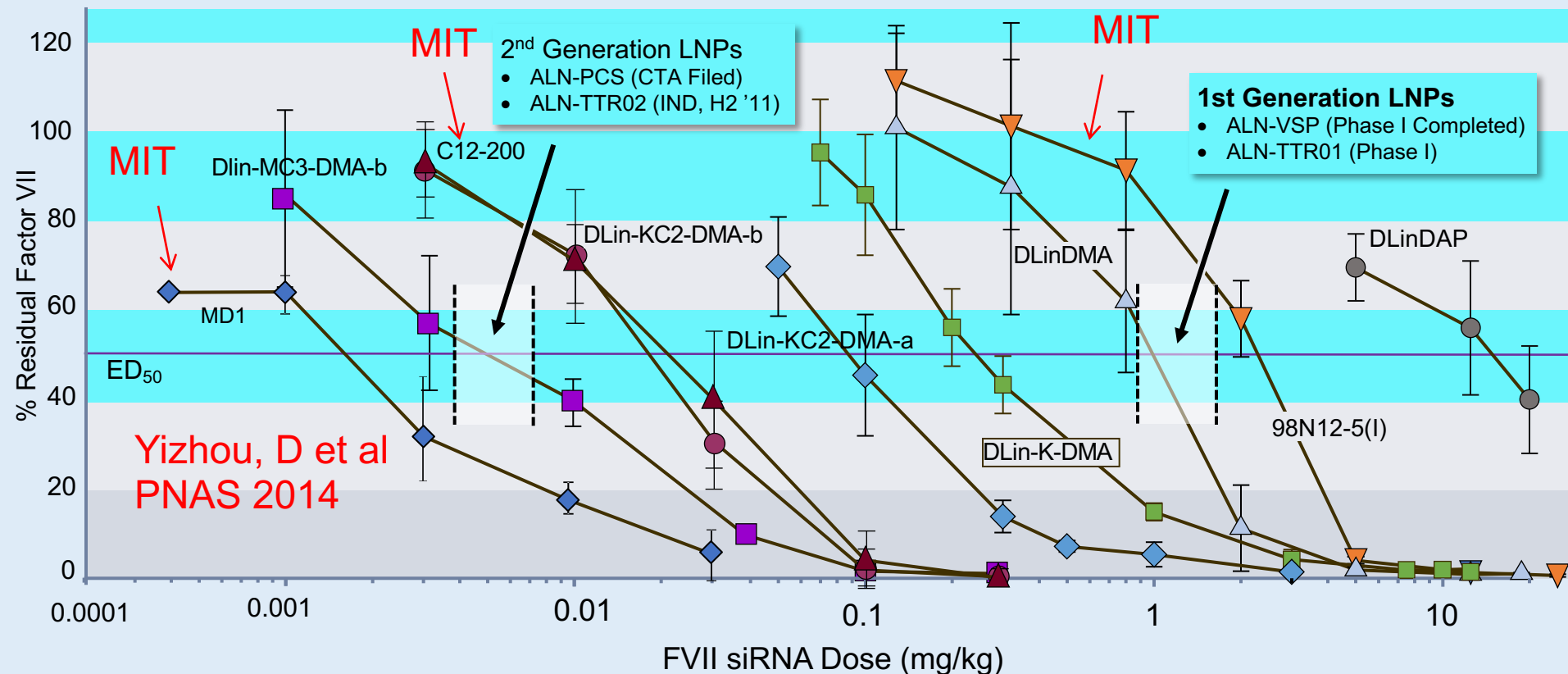


# *Single dose knockdown of TTR in Primates at $<0.03$ mg/kg*



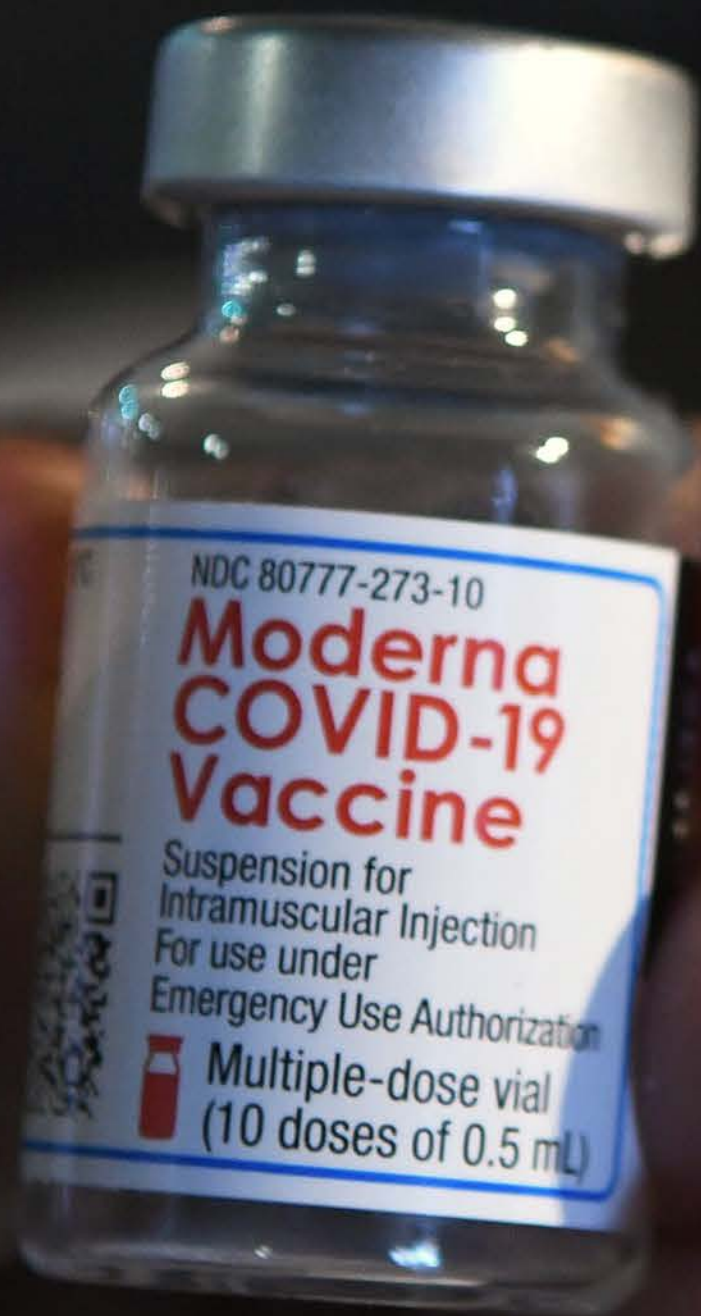
# Next generation LNPs: Remarkable potency improvements with novel lipids

- Novel LNPs set new benchmark for systemic RNAi with ~100 fold improved potency
  - Efficacy in pre-clinical models following single IV injection
  - Each LNP comprised of distinct cationic lipid component
  - Improvements in potency has resulted in single digit /kg ED<sub>50</sub>









NDC 80777-273-10

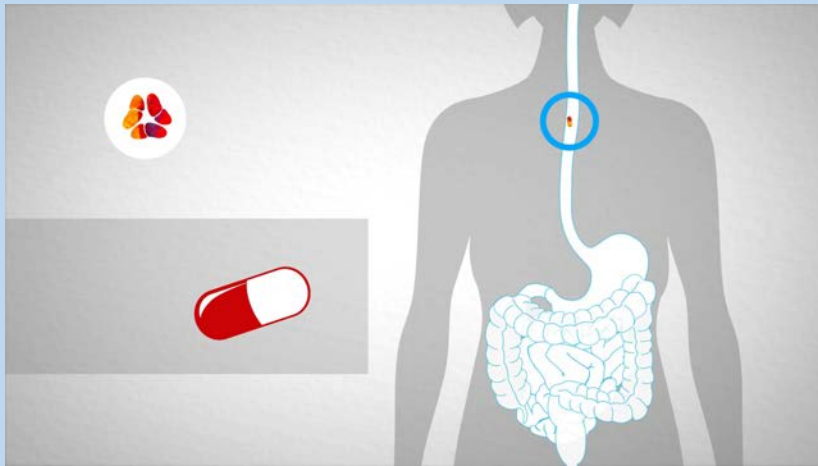
**Moderna  
COVID-19  
Vaccine**

Suspension for  
Intramuscular Injection  
For use under  
Emergency Use Authorization

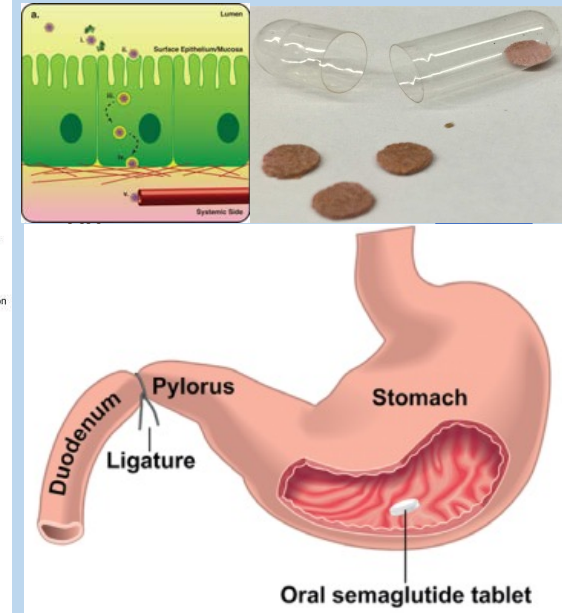
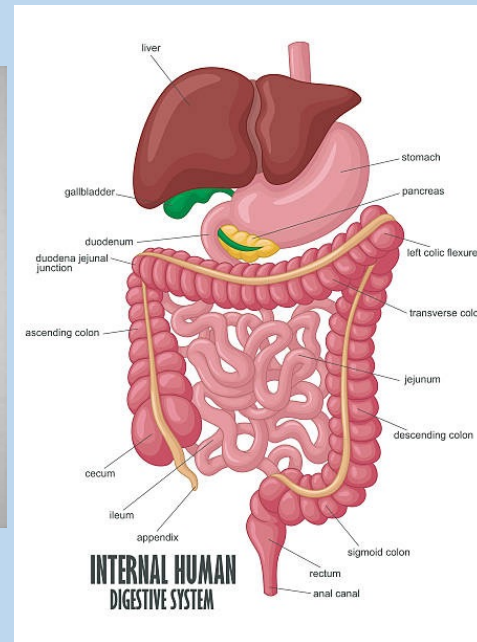


Multiple-dose vial  
(10 doses of 0.5 mL)

# Diffusion and degradation limits macromolecule uptake in the GI tract



Tibbett, M. et al *J.A.C.S.* (2016).  
Banergee, A. et al *Bioeng Transl Med* (2016).  
Buckley, S. et al *Sci Transl Med* (2018).

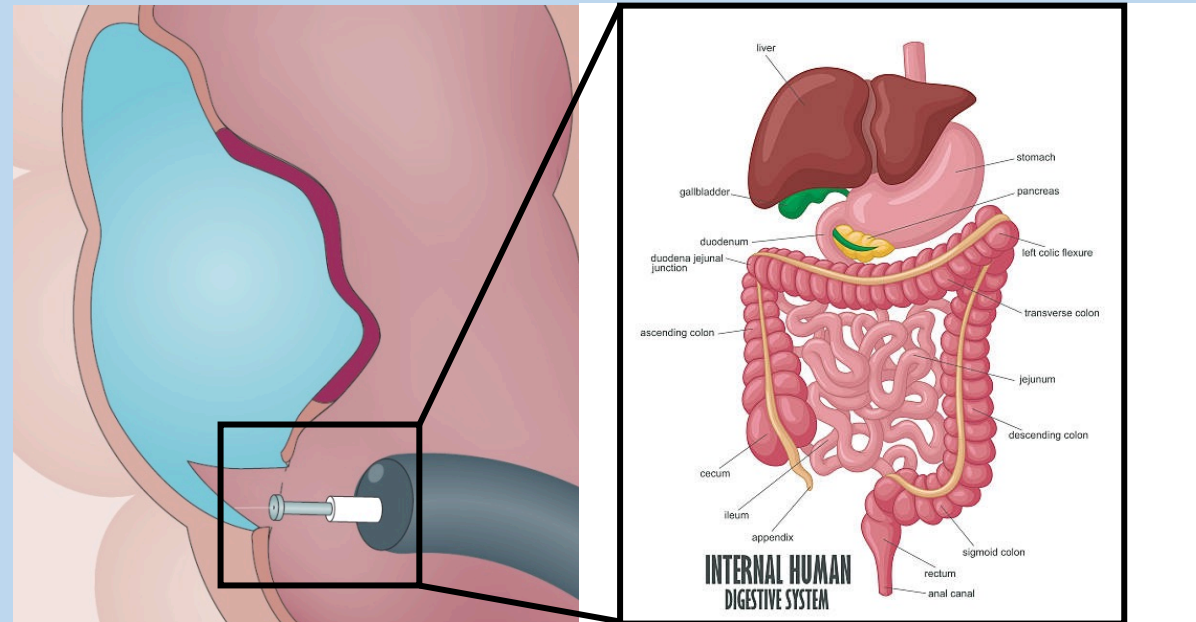


Davies, M. et al *JAMA* (2017).

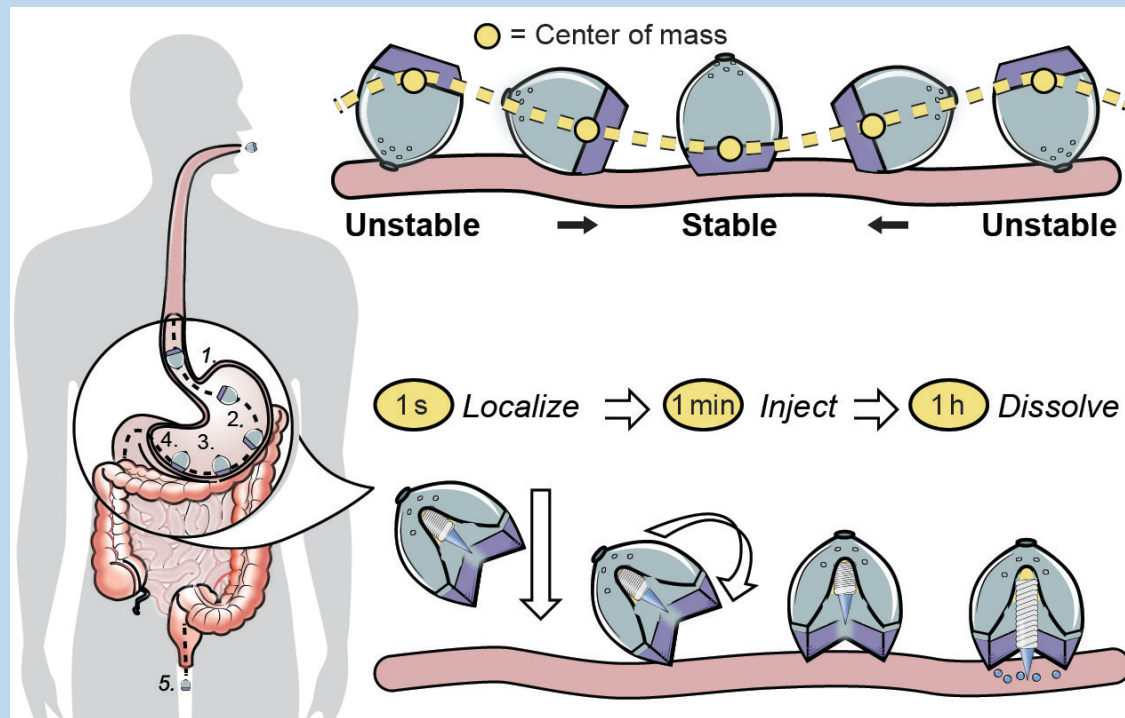
# Injectons can deliver drugs to the gut

1. High delivery efficiency
2. No painful sensations
3. Rapid tissue regeneration

Saunders, B et al *Nat Rev Gastroenterol. Hepatol.* (2016)



# Device Concept: Self-Orienting



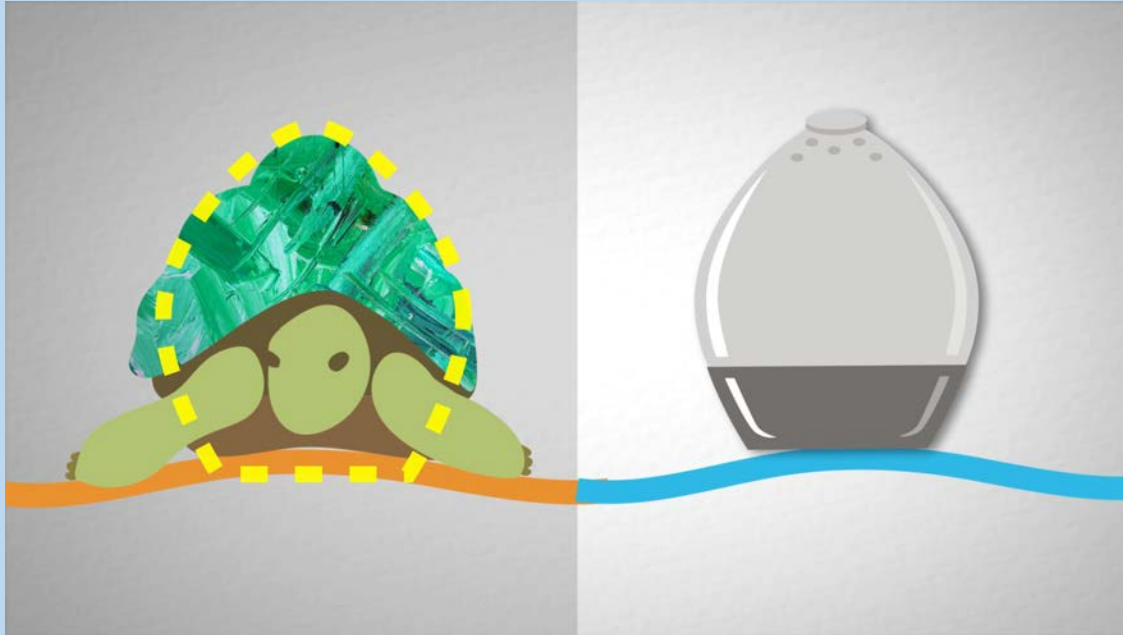
Device Requires:

- Tissue wall localization
- **Self-Orientation**
- Safe and Efficacious Actuation
- Clinically Relevant Dose Size

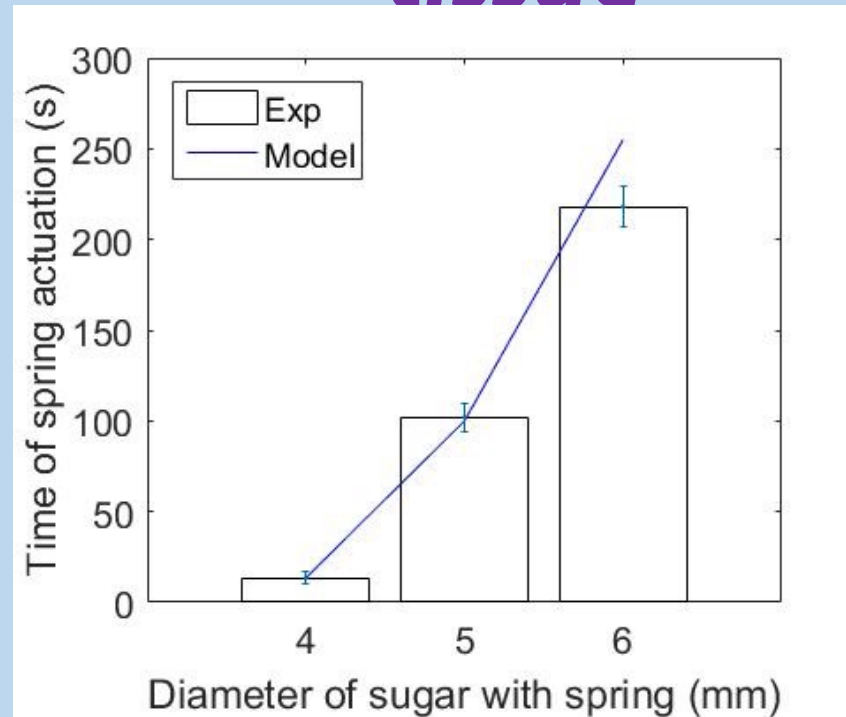
Abramson et al., *Science* (2019)



# *Self-Orienting: Inspired by the Leopard Tortoise*

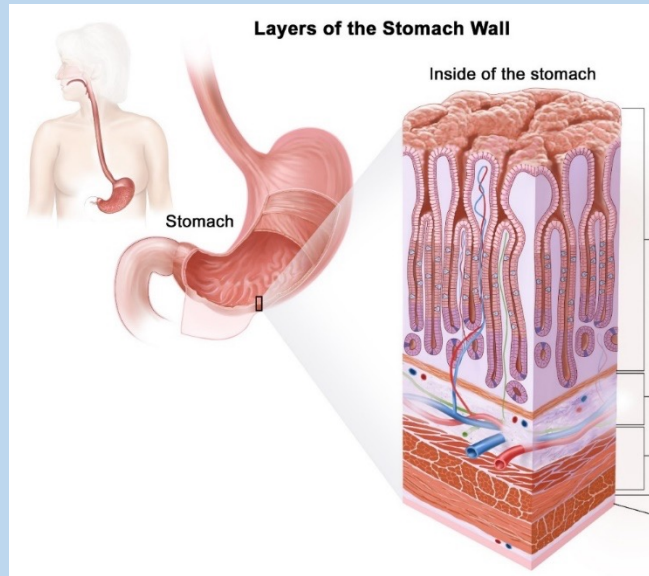


# ***A hydration based actuator and a compressed spring drives drug into tissue***



*Because sugar is brittle, it releases the spring in 1 ms*

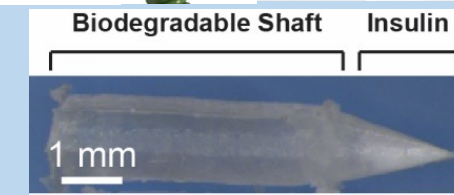
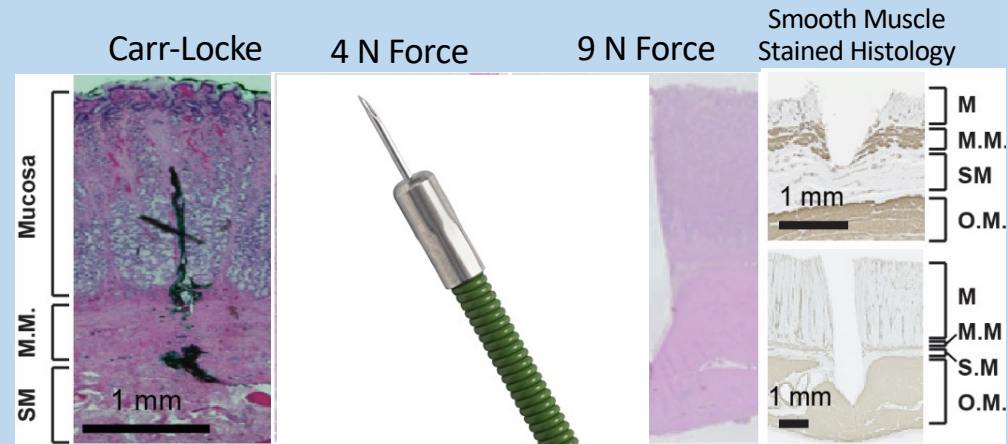
# Perforation risk is mitigated by controlling actuation force



[www.cancer.gov](http://www.cancer.gov)

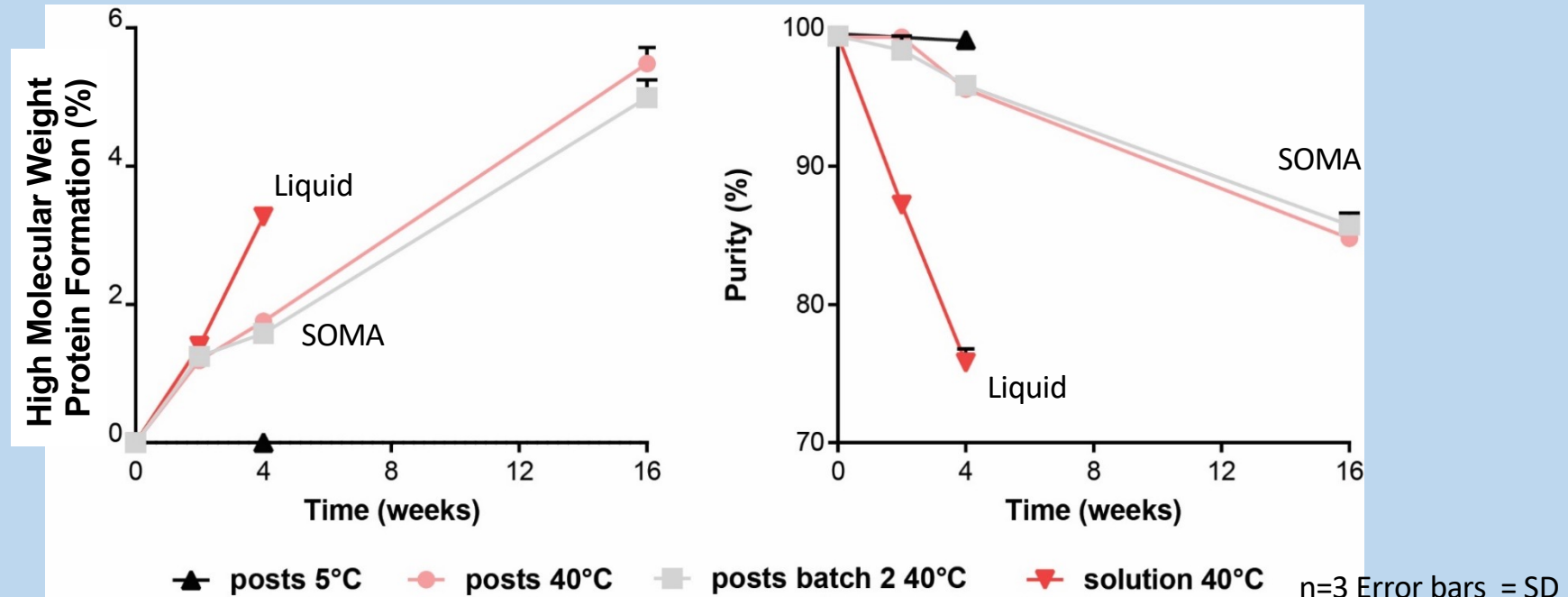
Mucosa

Submucosa  
Muscle  
Serosa



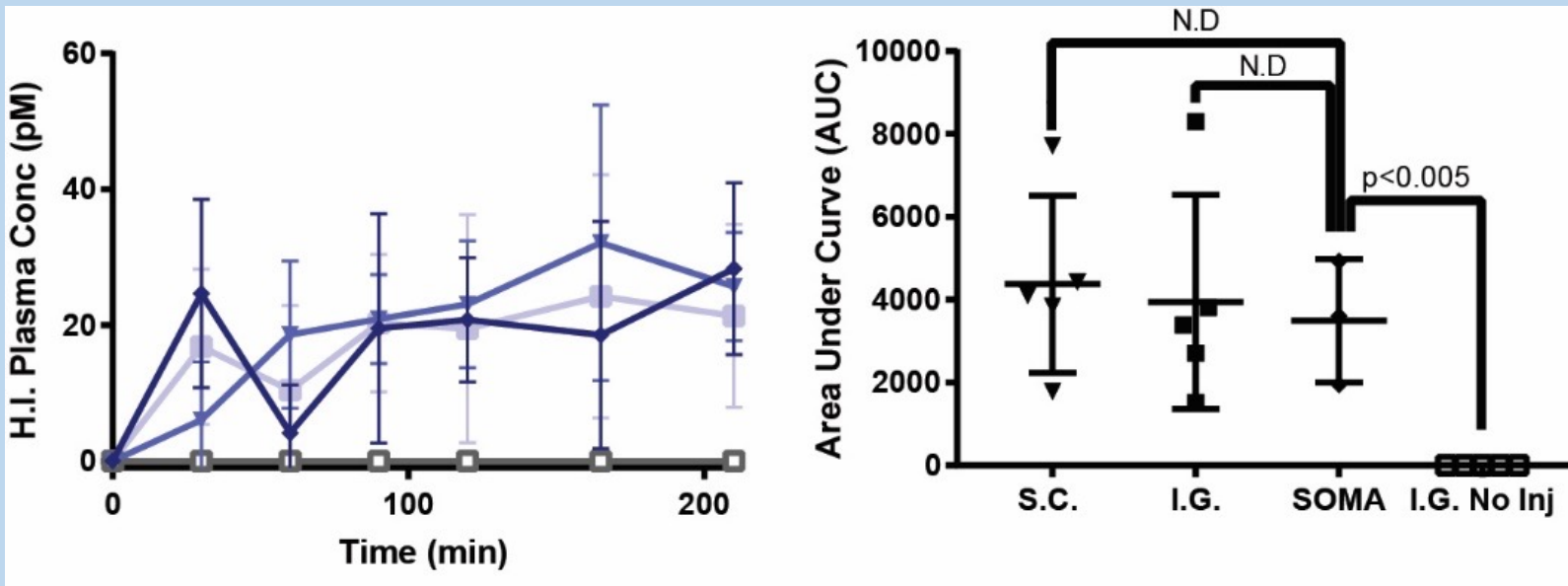
SOMA Drug Post

# *SOMA Insulin is stable for up to 4x longer than a liquid formulation*



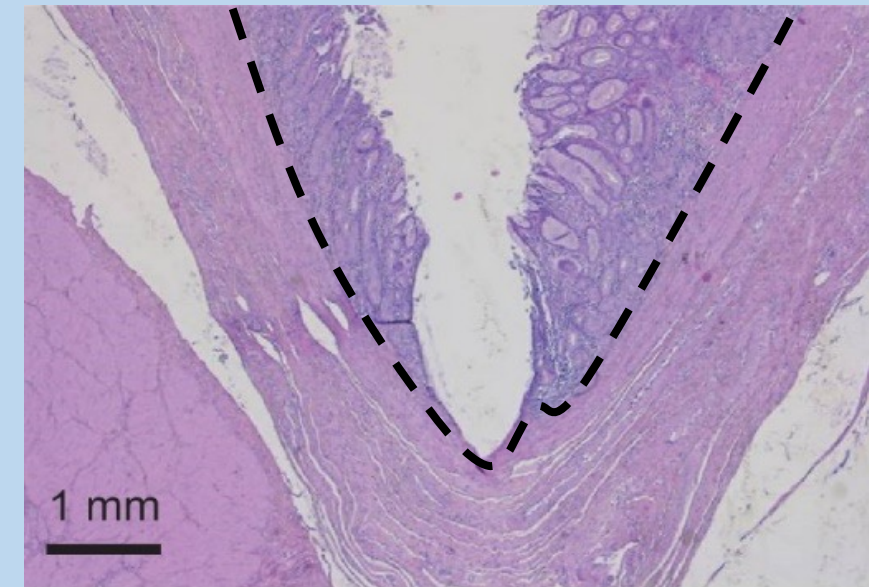


# SOMA insulin delivery yields similar uptake to subcutaneous injections



Muscle

Mucosa

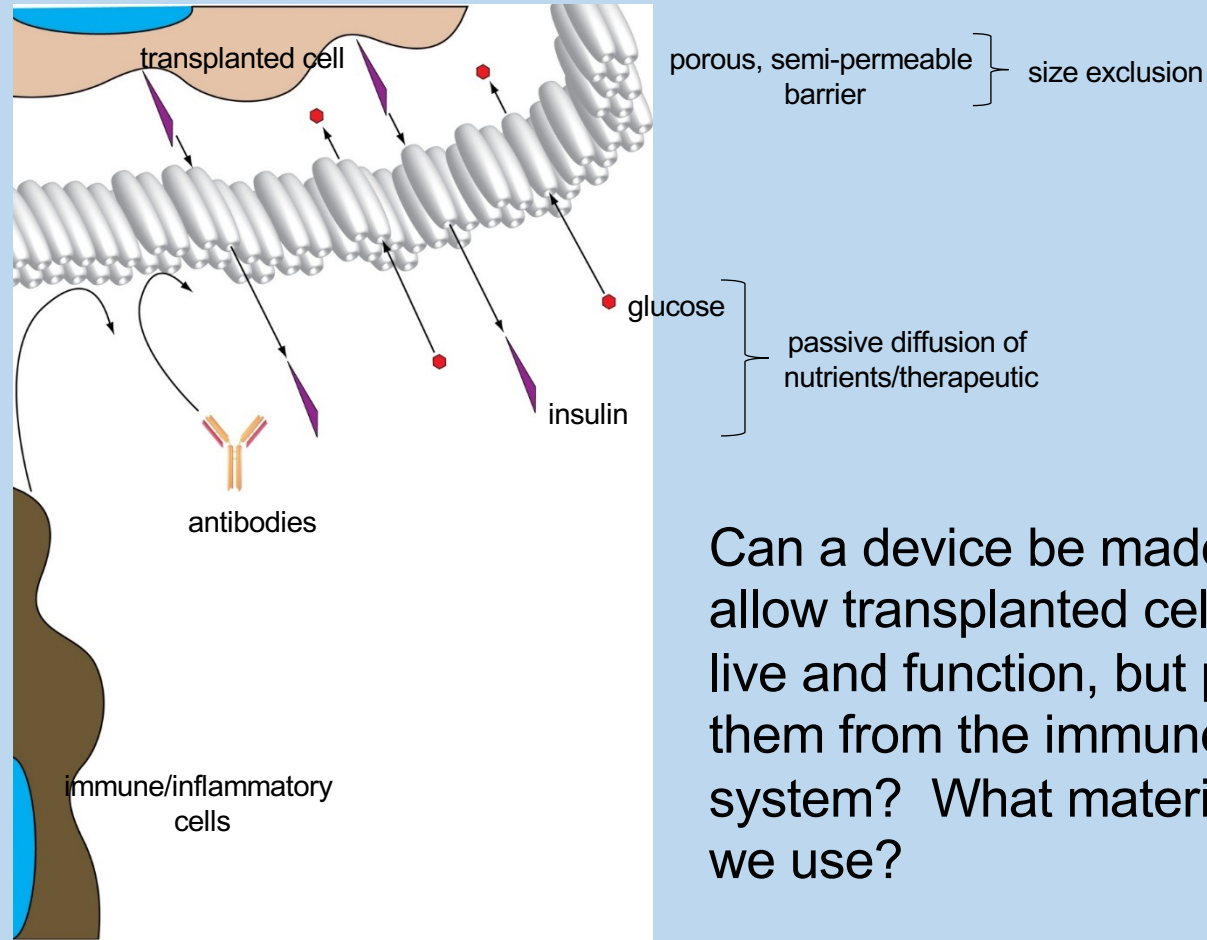


Abramson et al., *Science* (2019)



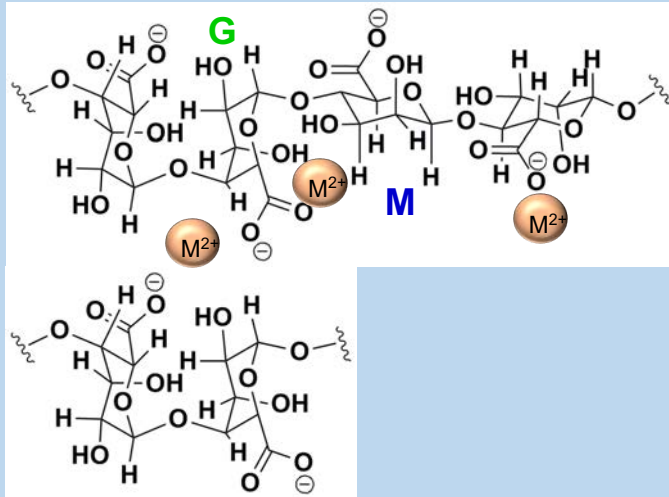
Error Bars = SD

# Cell encapsulation: Can cells be protected with materials?

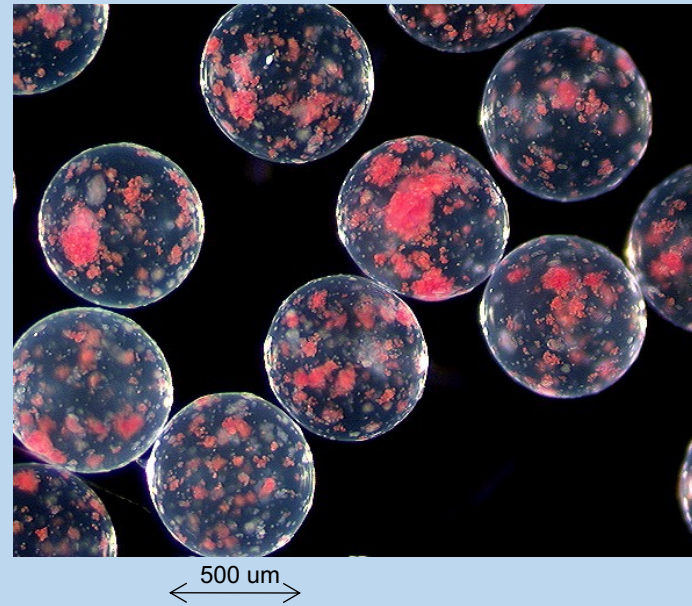
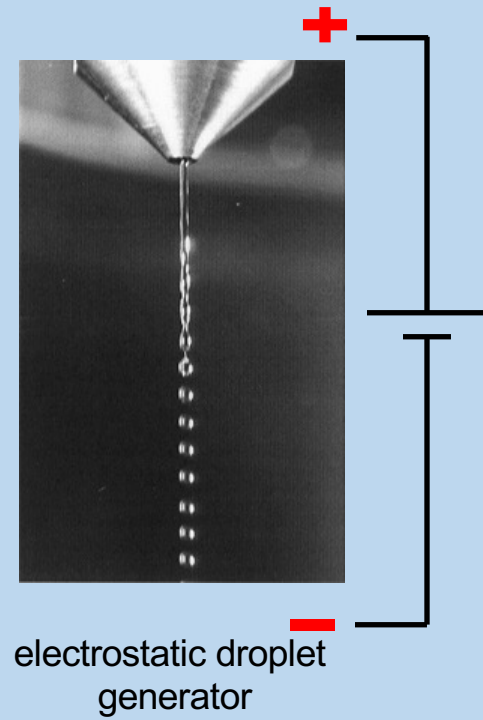


Can a device be made to allow transplanted cells to live and function, but protect them from the immune system? What material will we use?

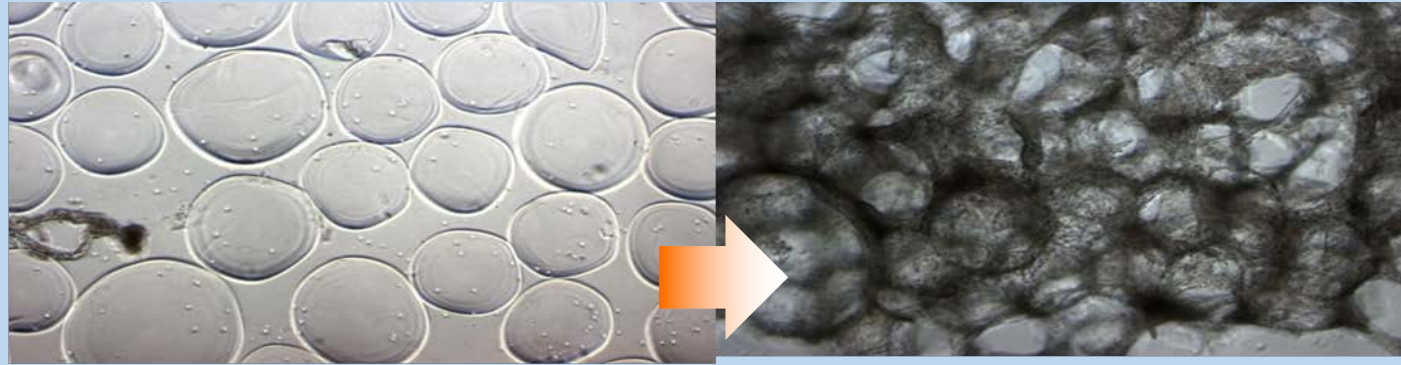
***Only a few materials have been investigated – most work has been with alginate from seaweed***



# *Islet encapsulation in alginate microbeads*



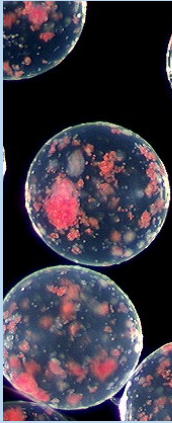
# *Transplanted, encapsulated islets become covered in scar tissue*



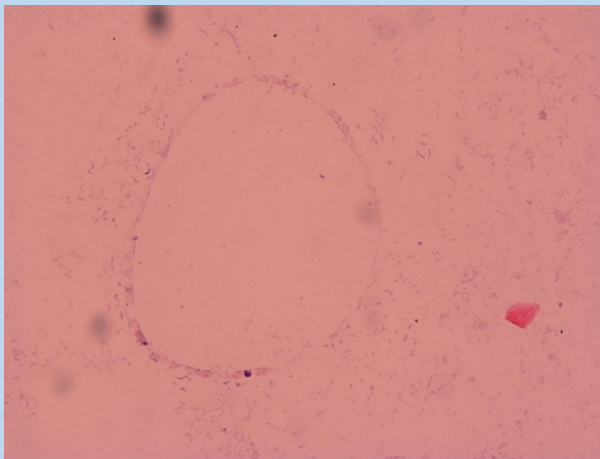
- Alginate is not sufficiently biocompatible and is recognized as a foreign material
- Can we develop materials that keep cells alive and functioning but do not get covered in scar tissue?



# Conventional Ba<sup>+</sup> alginate capsules fibrose in a manner dependent on Strain



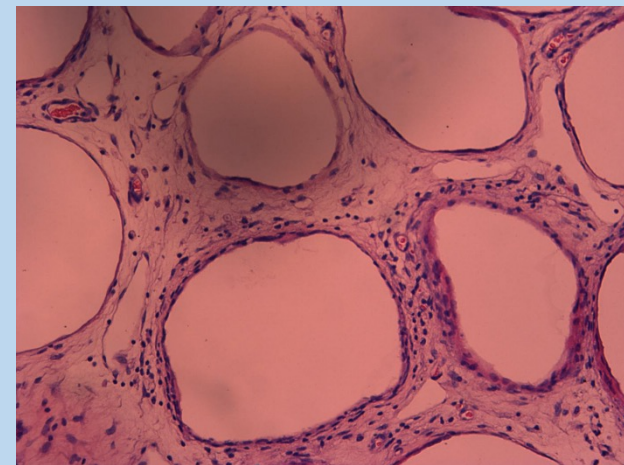
1 week



**Non-Diabetic Animals:**  
**BalbC Mouse – Clean**  
**Lewis Rats –Clean**  
**B6 Mouse – Fibrosed**  
**Cynomolgus– Fibrosed**  
**Baboon – Fibrosed**

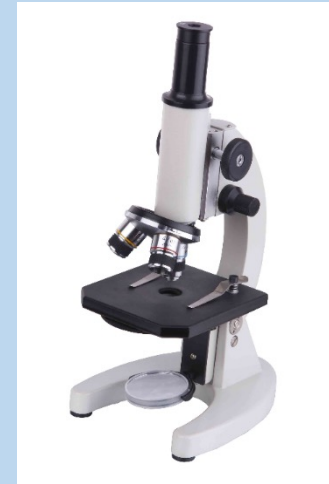
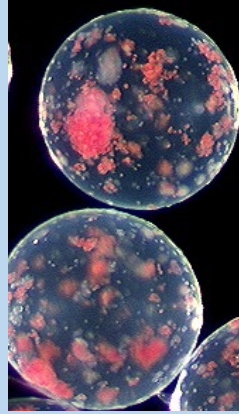
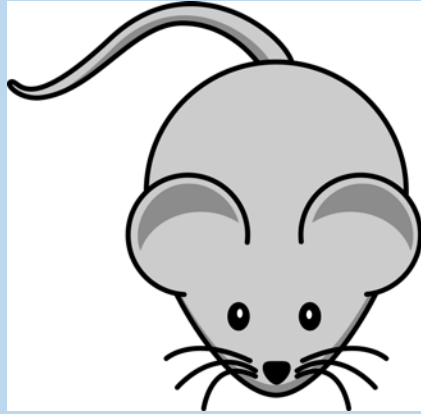
*Anderson, Weir,  
Greiner, et al.*  
+  
*Jose Oberholzer  
Meirigeng Qi  
UNPUBLISHED*

4 weeks



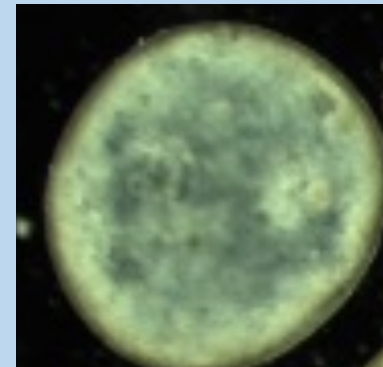
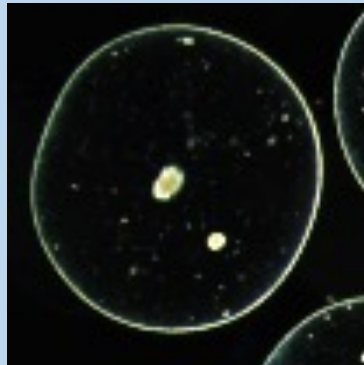
How can we evaluate this faster?

# ***Gold standard: Examine retrieved capsules***

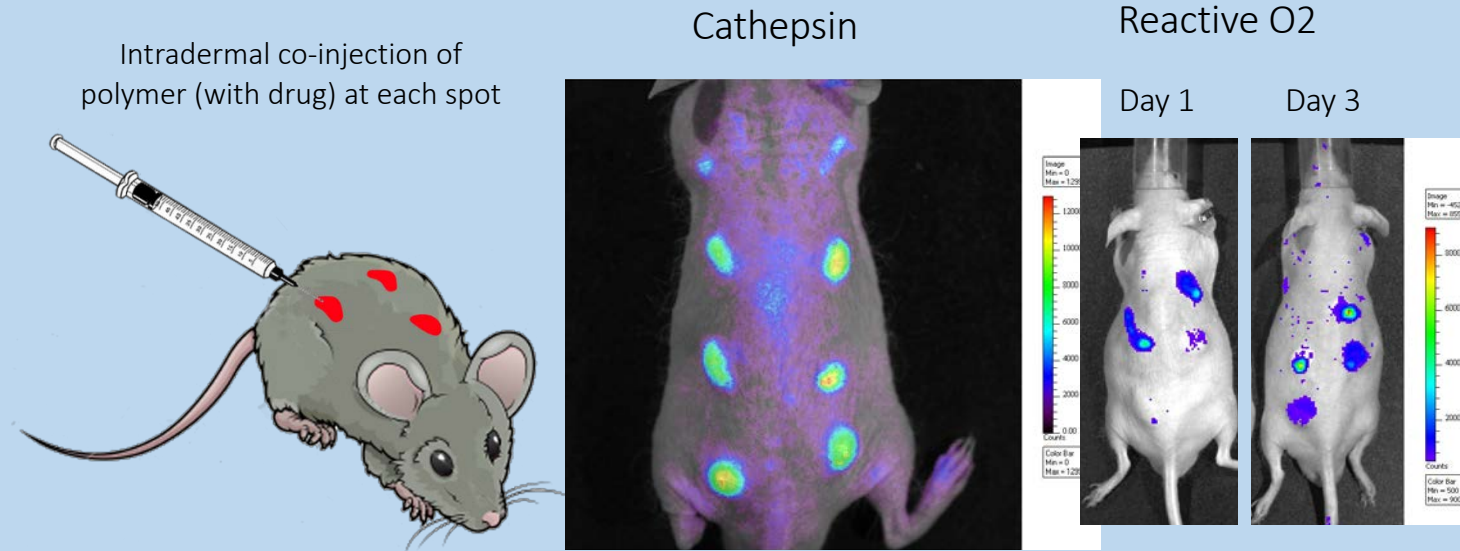


Strong correlation with success

Device failure



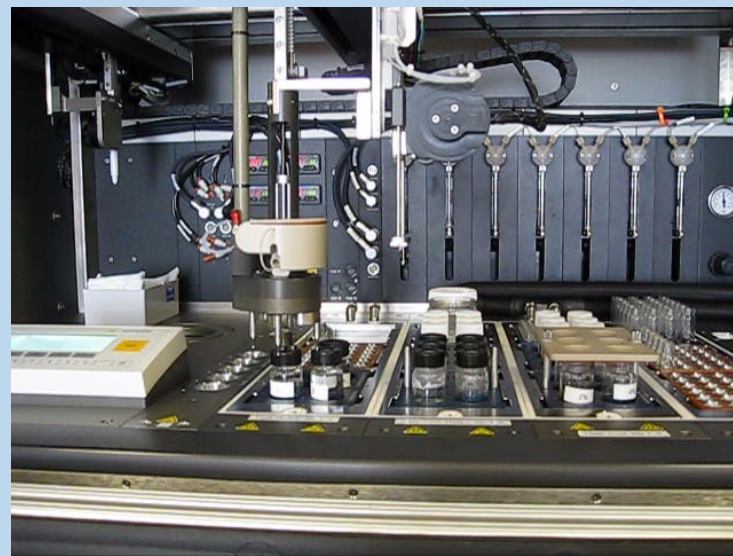
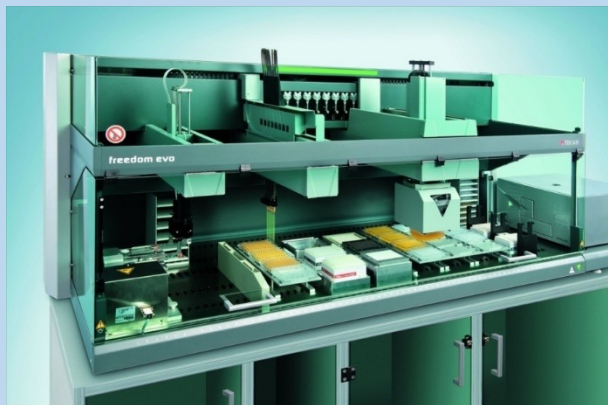
# *Transcutaneous imaging of inflammation response to multiple devices per animal*

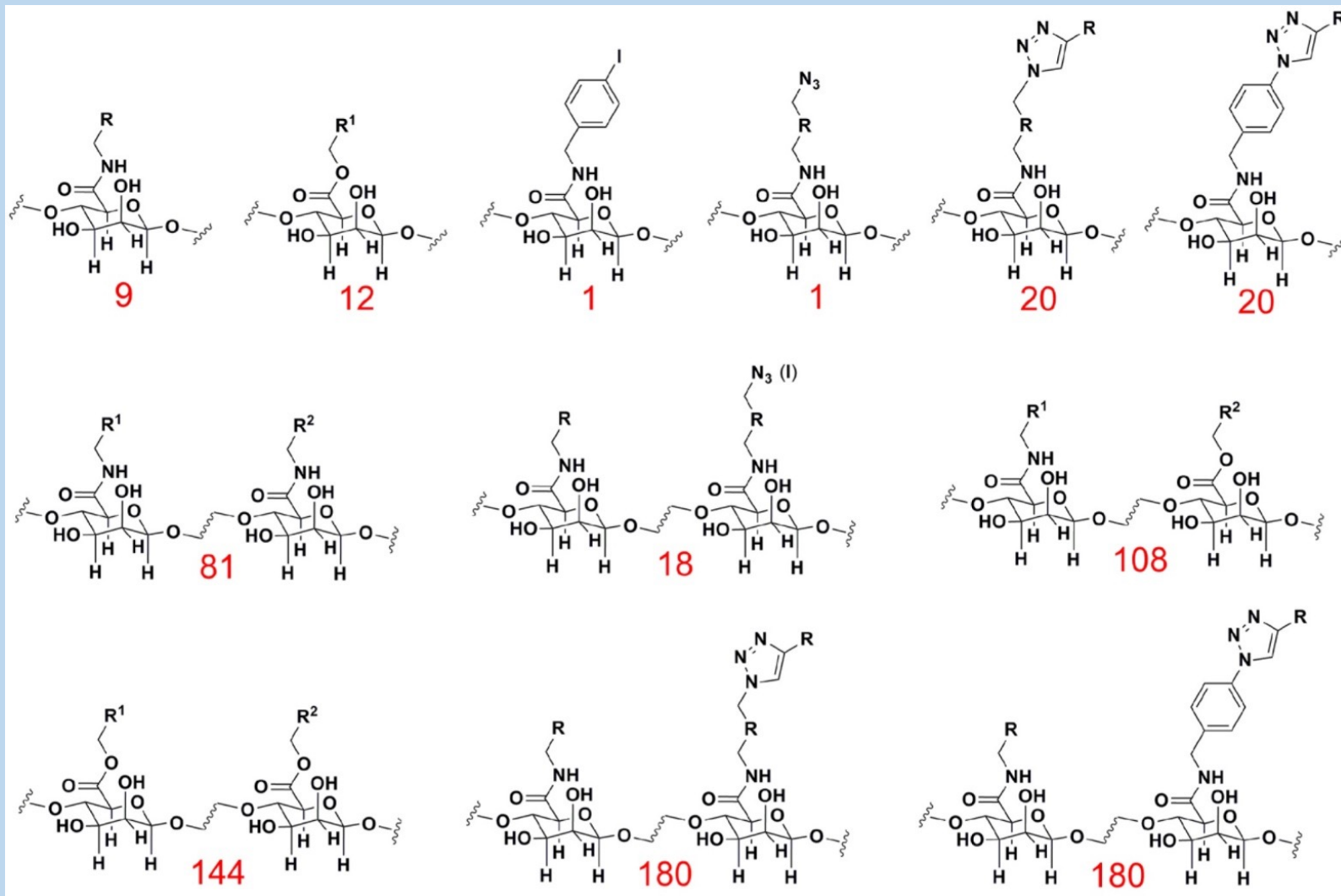


How do we build a pipeline for new material development for islet transplantation?



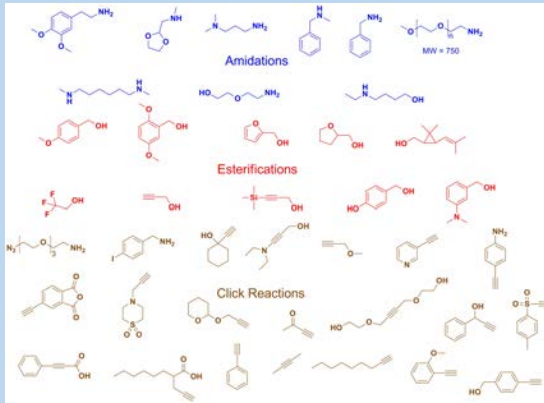
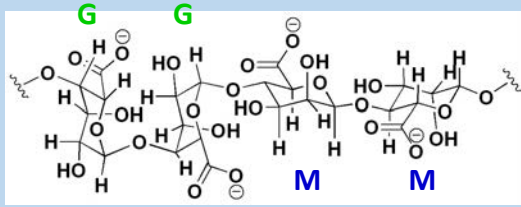
# *Automated, high throughput polymer synthesis*





Current progress for the alginate modification library.  
 Numbers indicate the number of unique, diverse alginates  
 that correspond to each general structure.

# Developing superbiocompatible materials for a tissue engineered pancreas



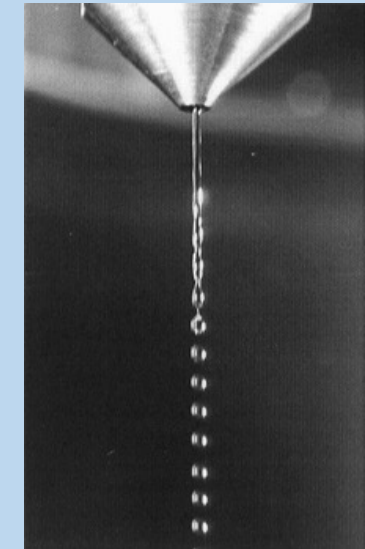
novel  
material design



automated,  
combinatorial synthetic execution



material  
characterization

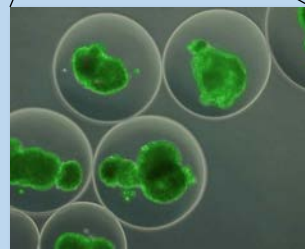
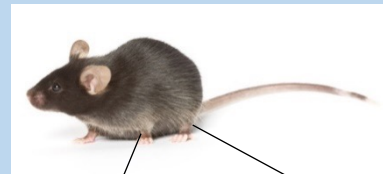


capsule formulation  
islet encapsulation

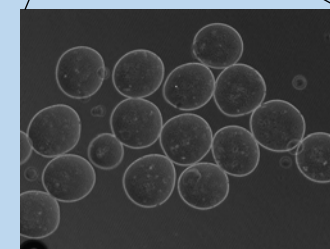
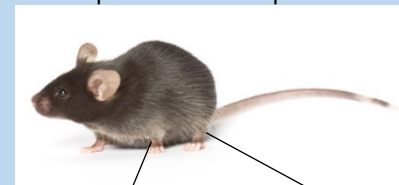
Large Animal Studies



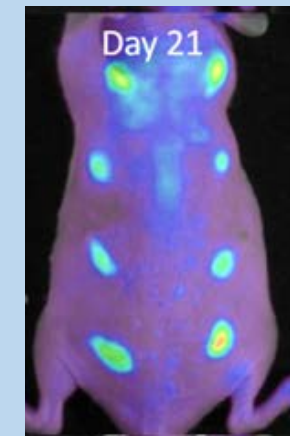
Encapsulated Rat  
Islets in Diabetic Mice



Capsule performance  
In peritoneal space



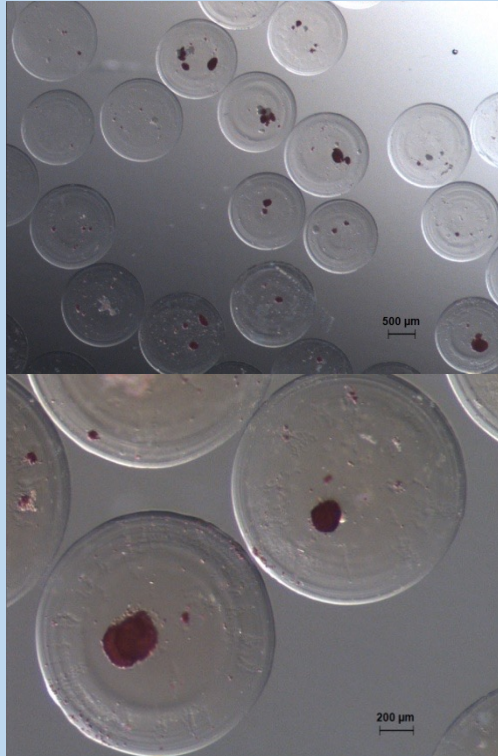
"High Throughput Mouse"  
Immune response





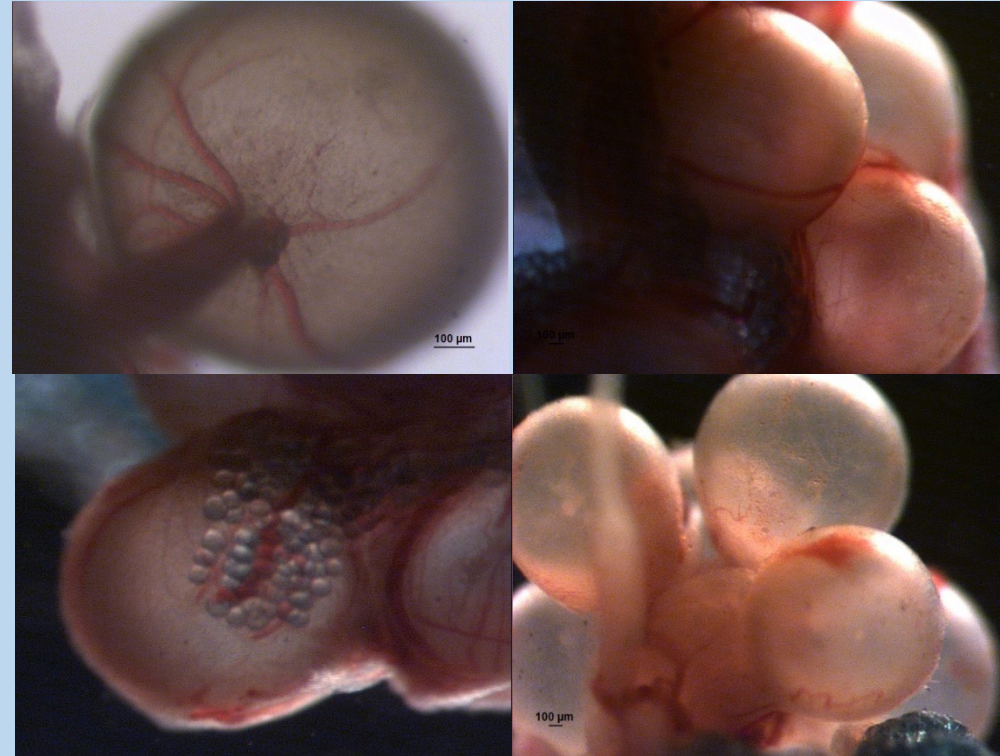
# Conventional alginate SLG20/TAM-ALLO-002 in non-human primates

Pre Transplantation



Uniform capsules  
Compact islets  
Cyno islets stain for dithizone

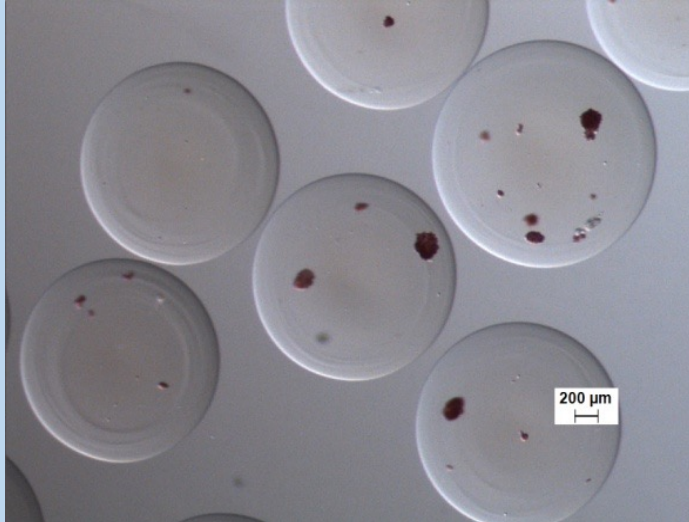
Post 4 week Retrieval



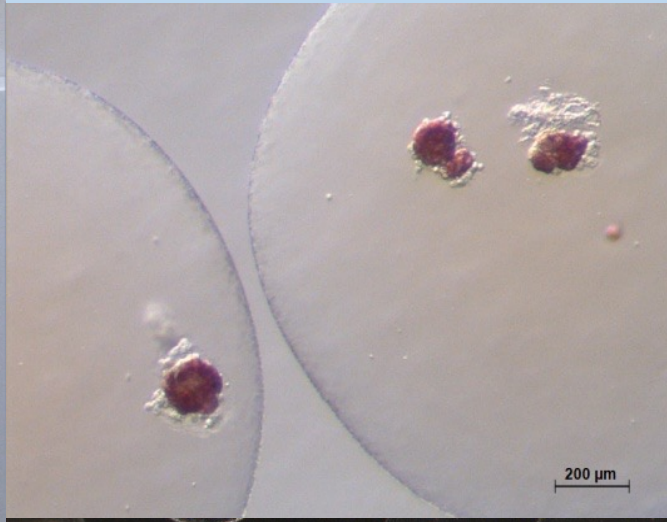
Capsule remains intact  
Fibrotic overgrowth observed on surface  
Severe Angiogenesis observed  
No islets present

# MIT-ALLO-003

Pre Transplantation



Post 4 week Retrieval

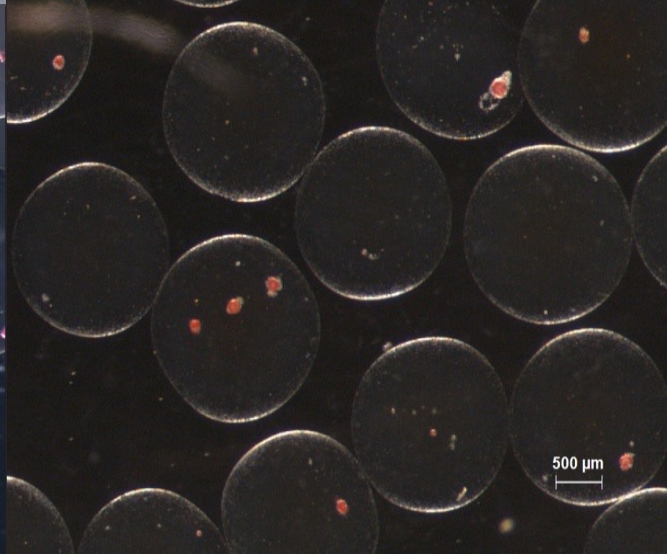
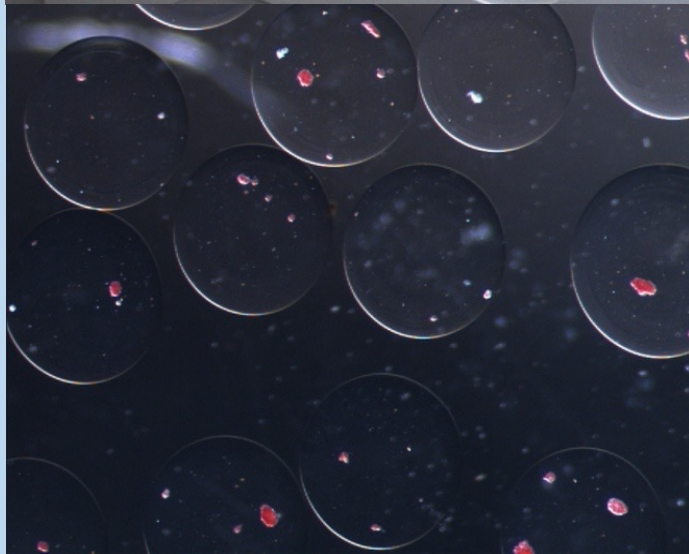


After 4 wk retrieval

Intact capsule

Compact islets

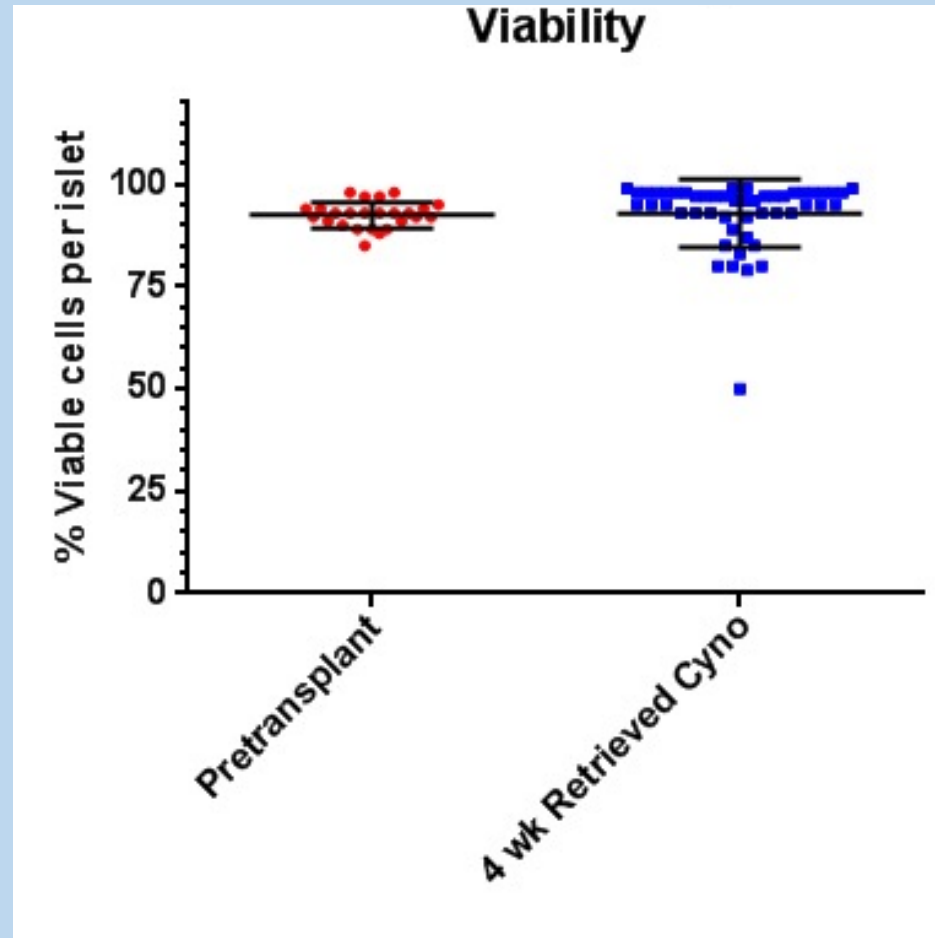
Cyno islets stain for dithizone



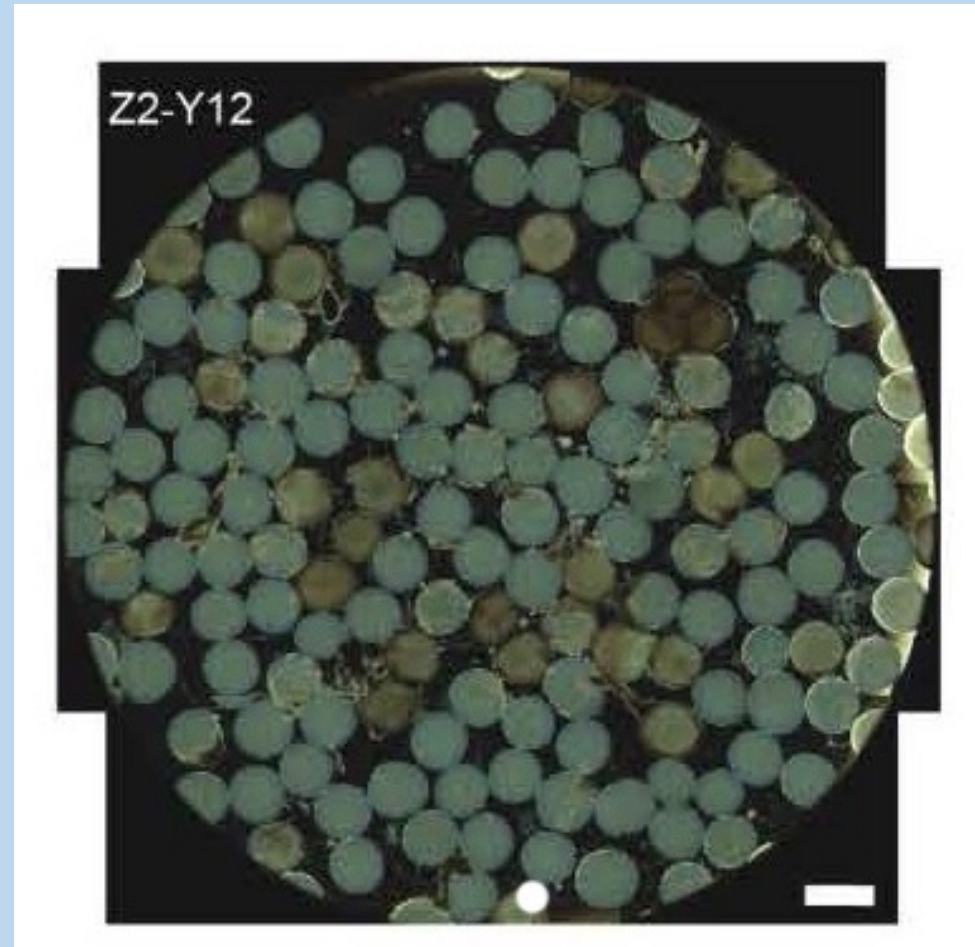
All capsules clean, non fibroses at 4 week retrieval

# Viability of MIT encapsulated cynomolgus islets after 4 weeks in primates

- Viability of encapsulated cyno islets assessed pre-transplant and 4 wk cyno retrieval
- FDA/PI viability stains to quantify percentage of viable cells per islet
- Pre-transplant  $n=25$ 
  - (92.5%  $\pm$  3.2)
- 4 wk Retrieved  $n=50$ 
  - (93.0 %  $\pm$  8.4)

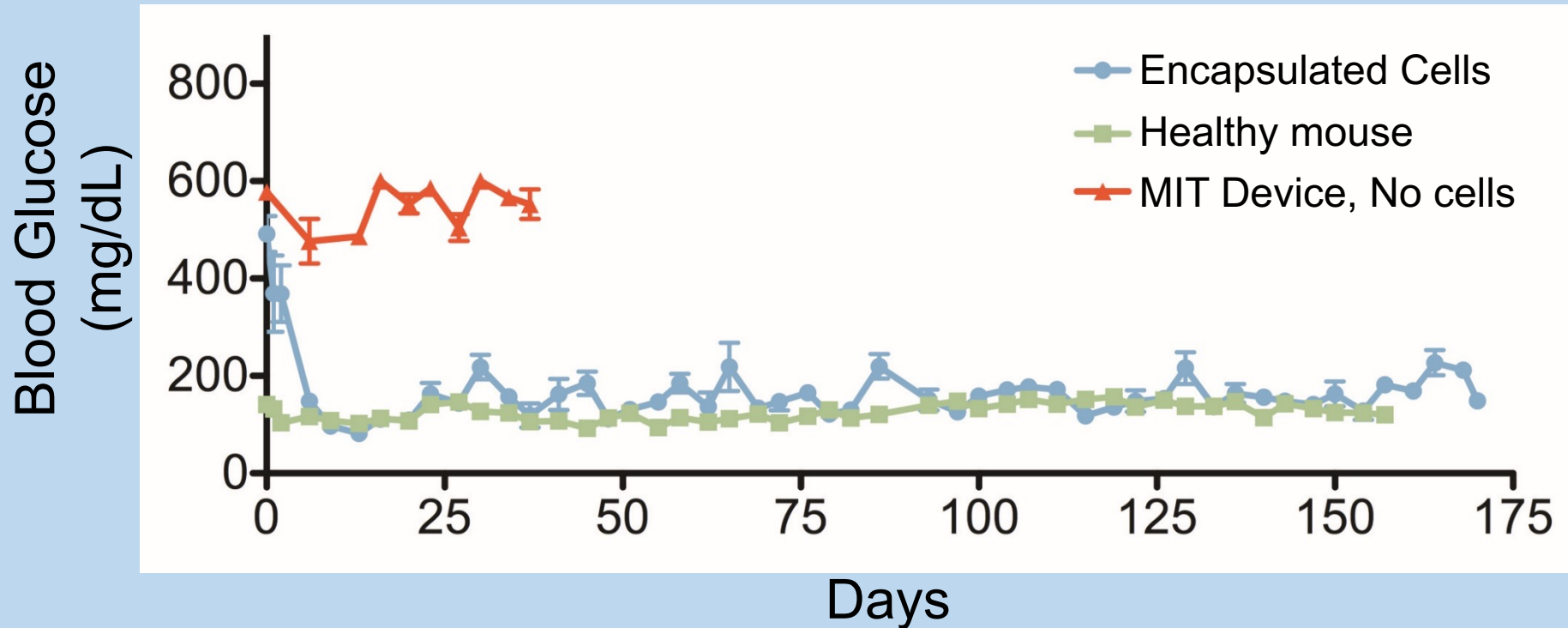






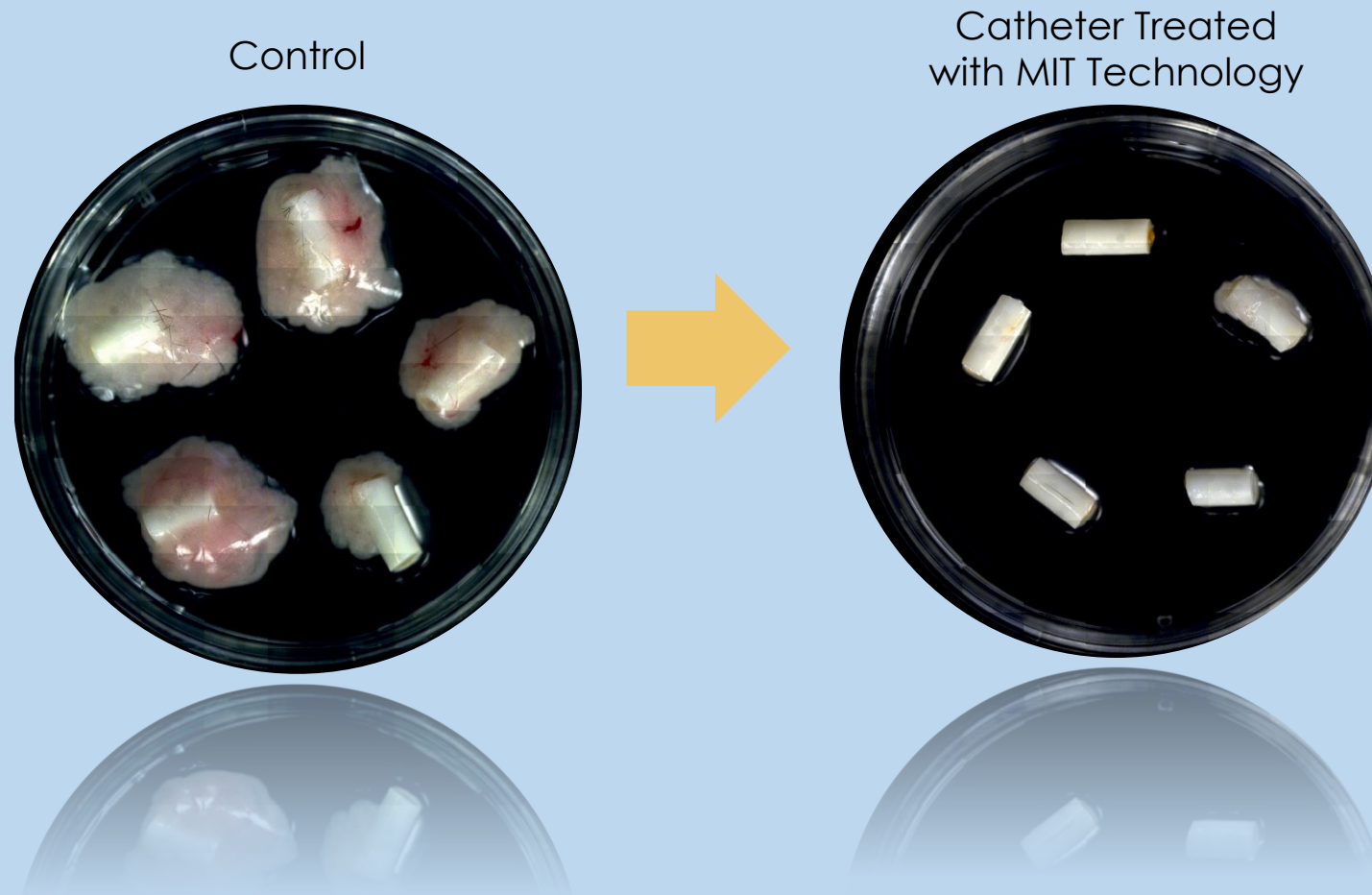
Representative phase contrast imaging after 6 months IP. Few macrophages and myofibroblasts are observed.

# *MIT encapsulation device in STZ treated B6 with HUMAN sc-beta cells*

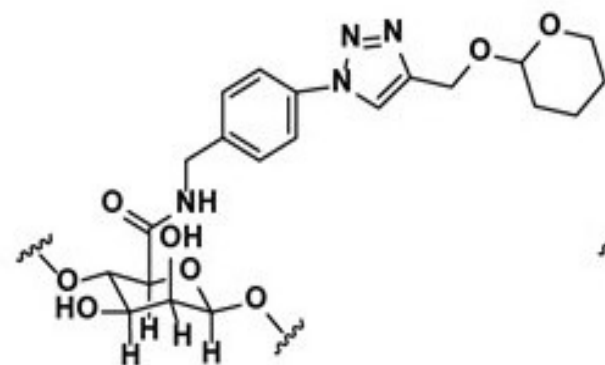




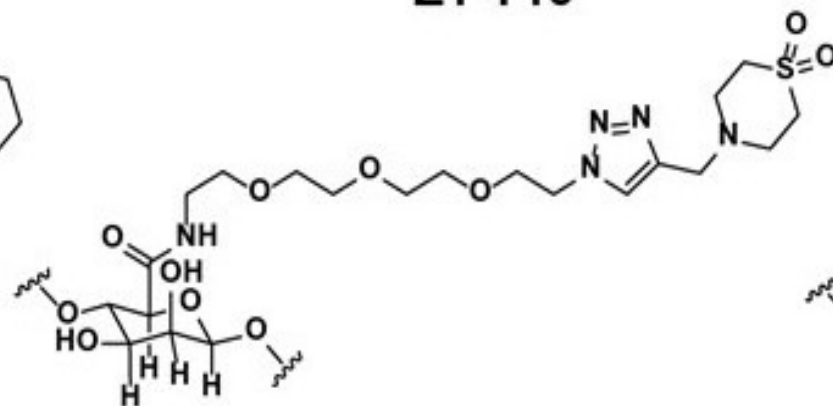
# *Peritoneal catheters modified by MIT polymers show no fibrosis after 12 weeks implantation*



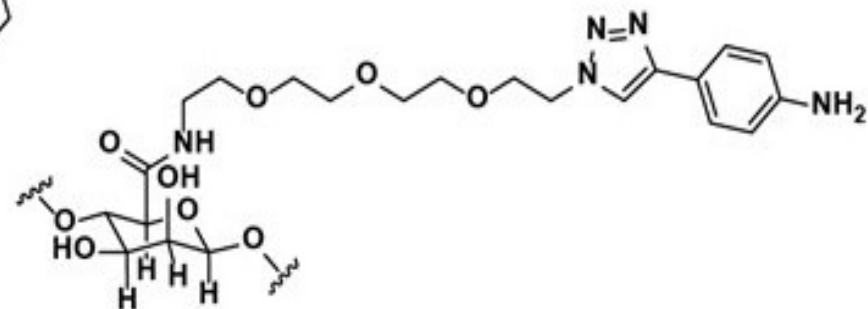
**Z2-Y12**



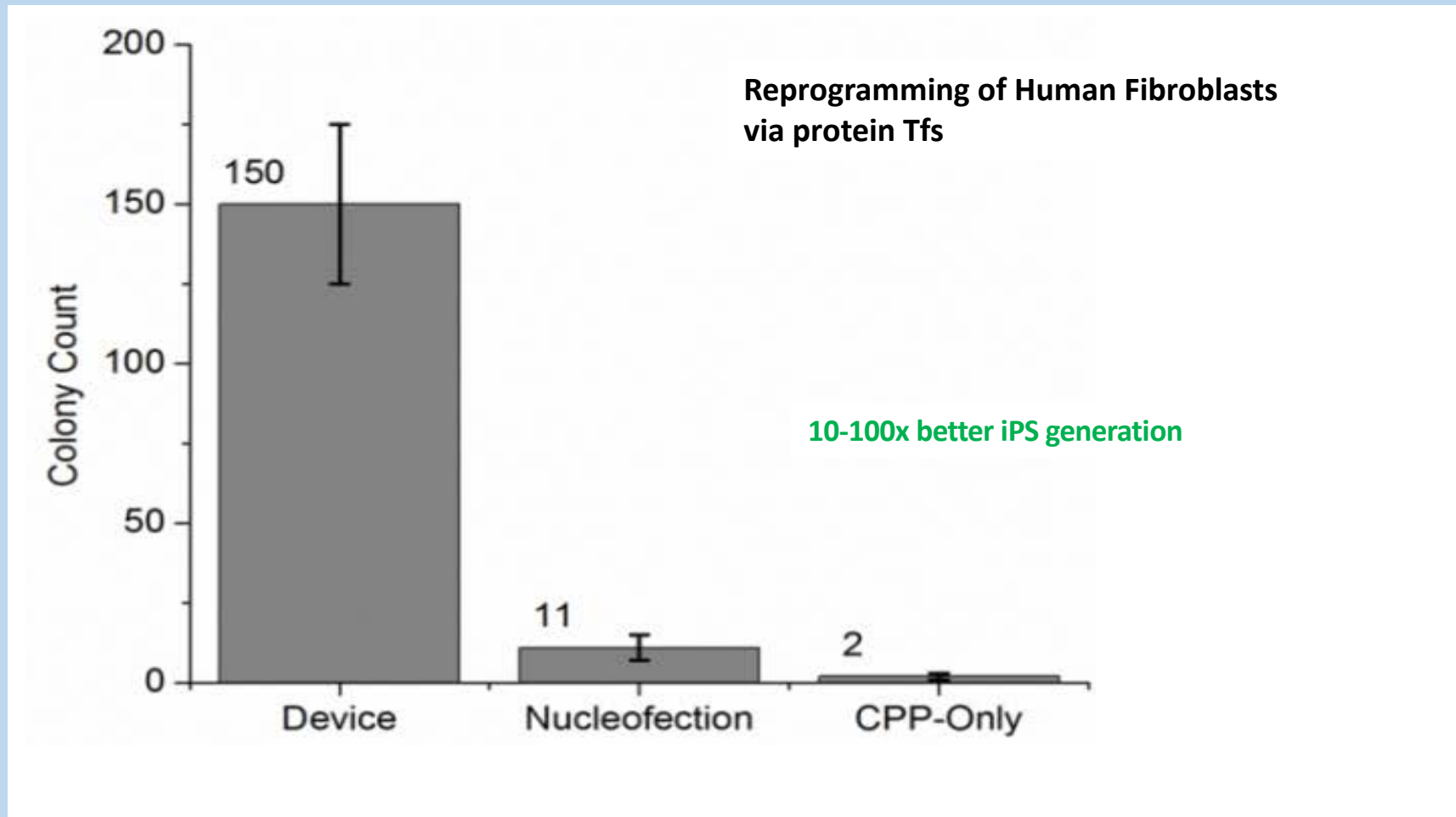
**Z1-Y15**

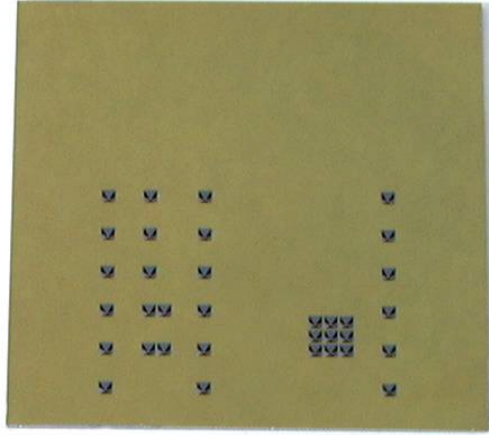
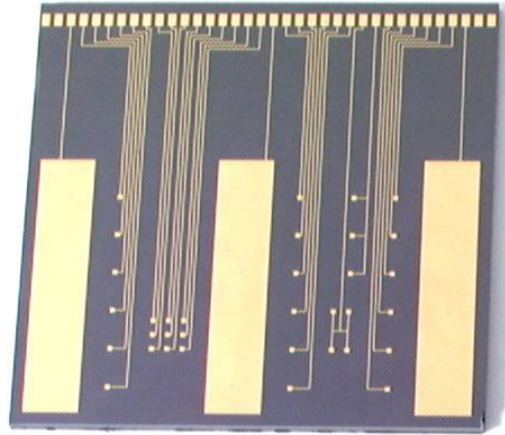


**Z1-Y19**



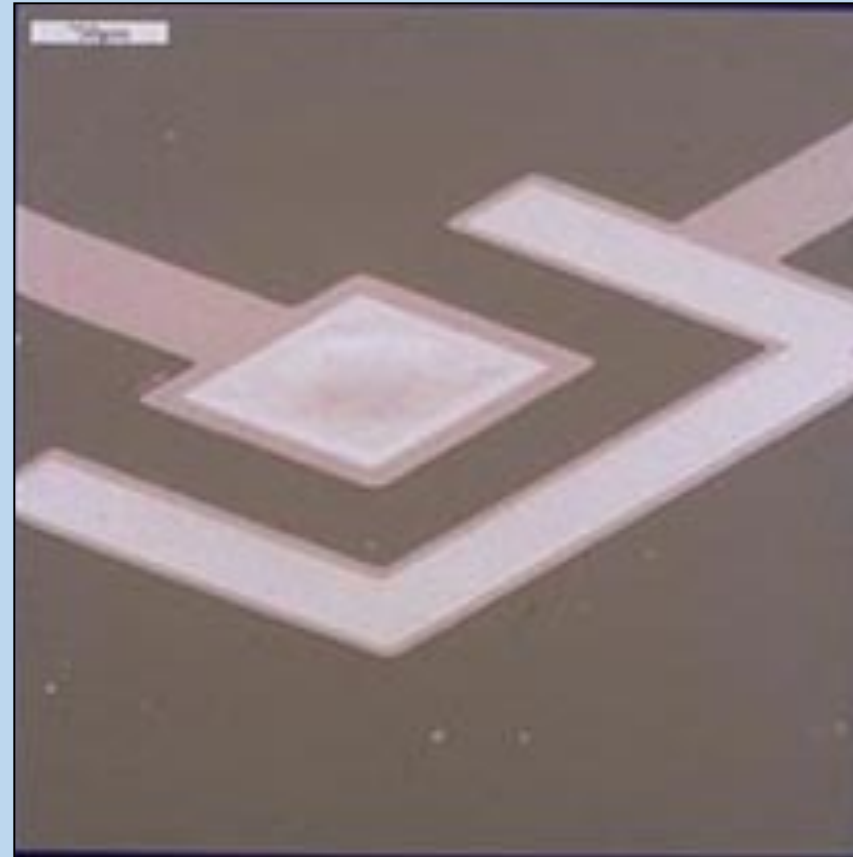
# Demonstrated efficacy in previously challenging applications



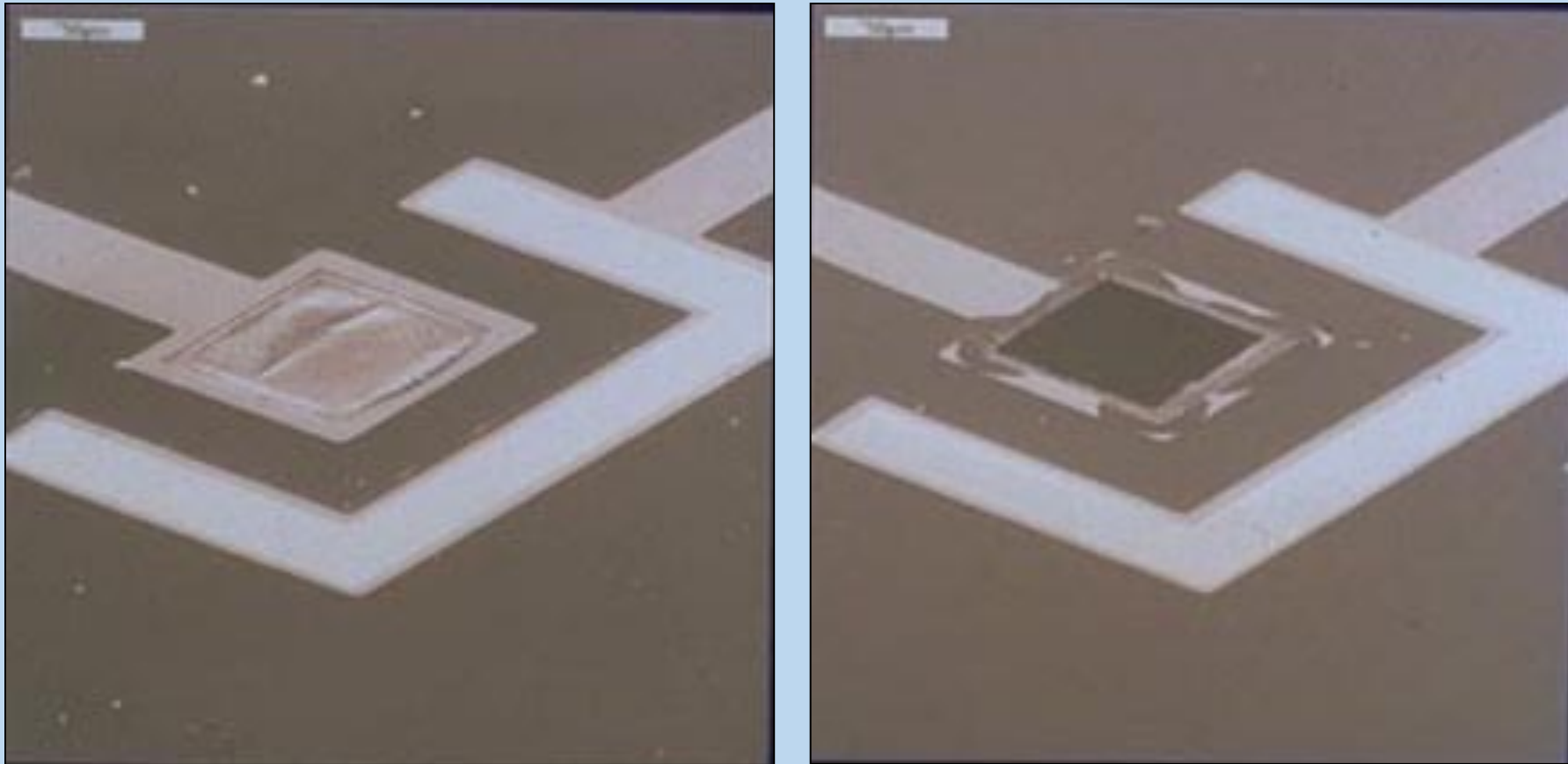


# ***Reservoir activation***

- SEM of a reservoir – electrode system before application of an electric potential

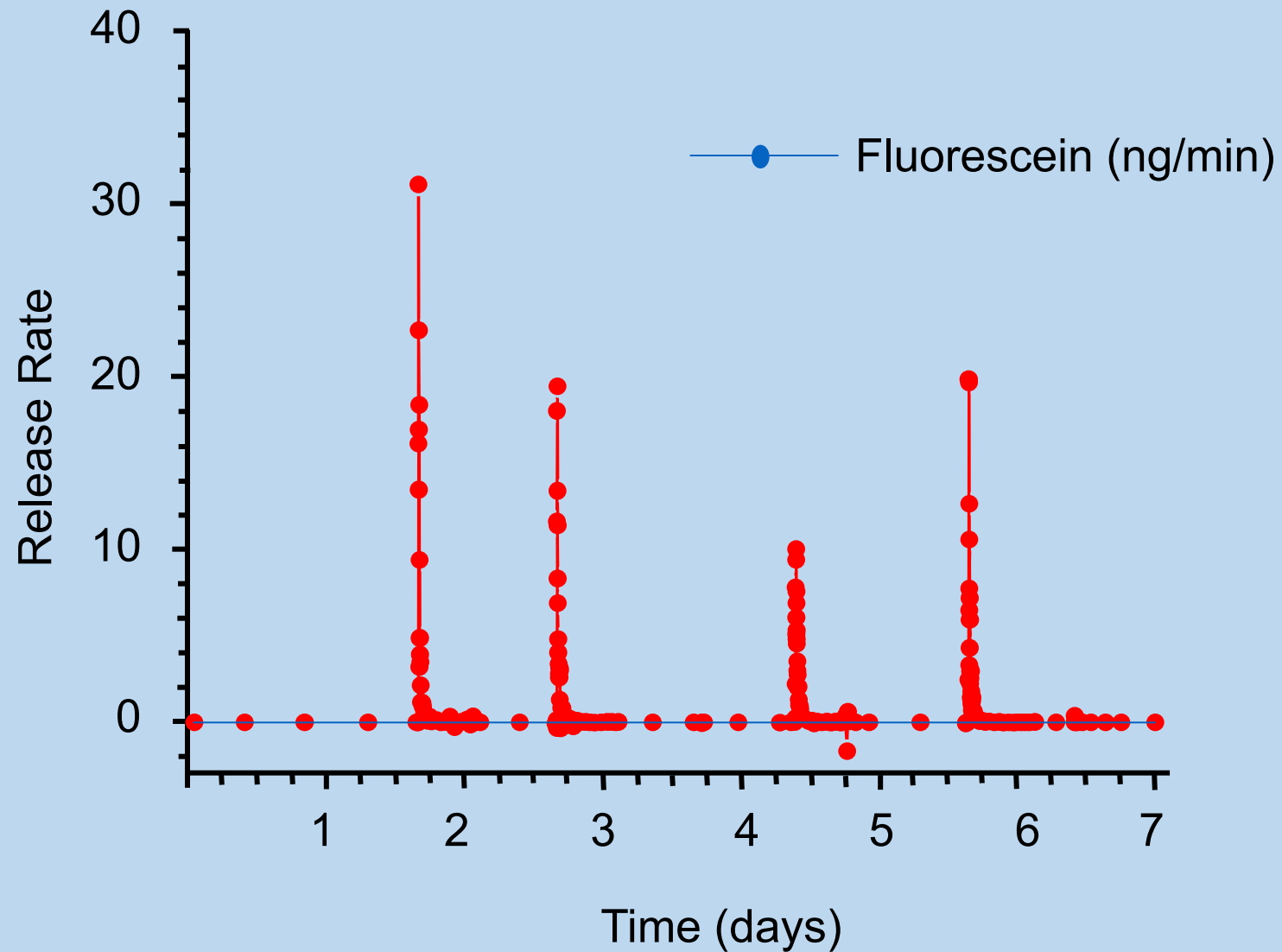


# *Reservoir activation*



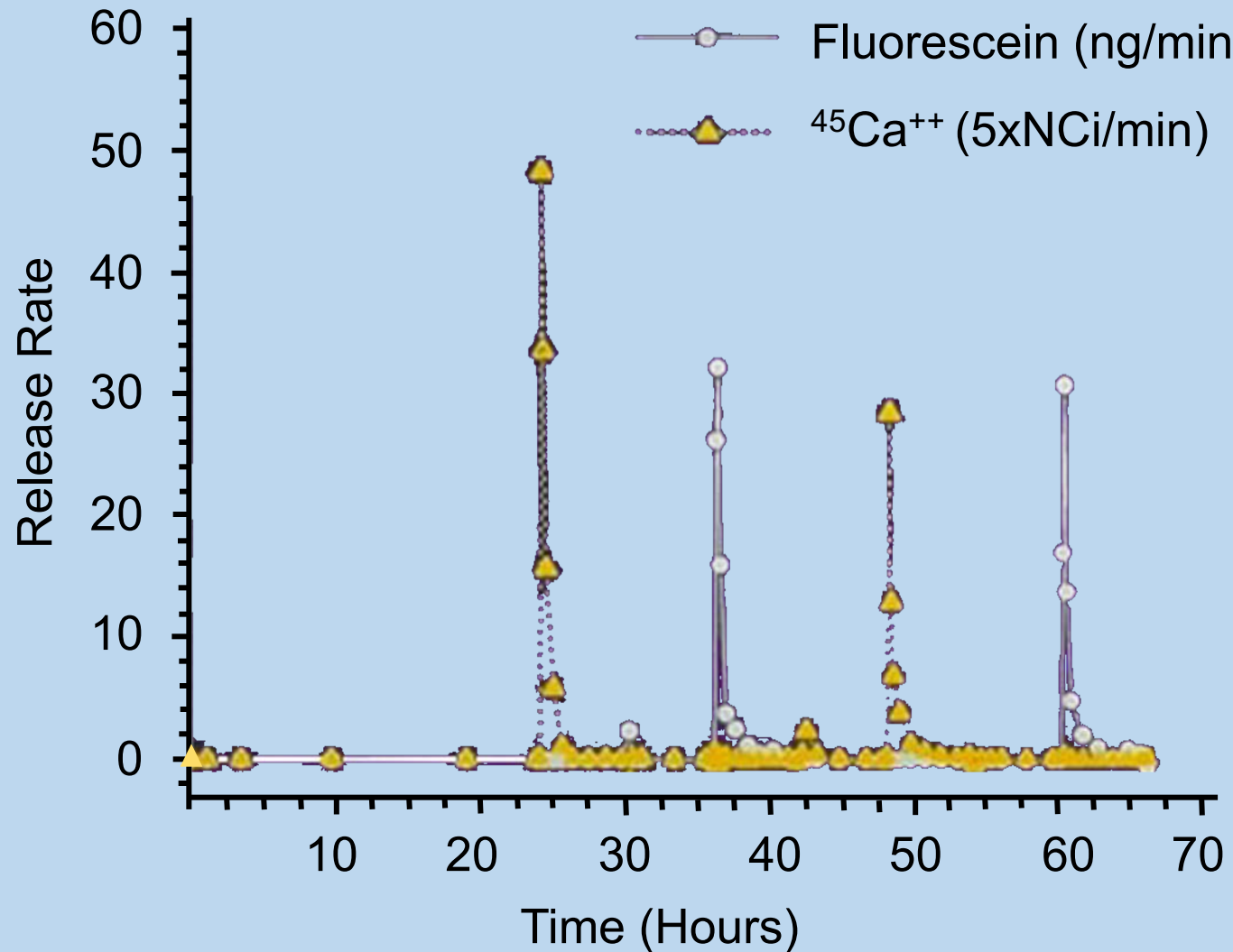
- SEMs taken after application of 1.04 volts vs. SCE in PBS

# *Single compound release*





# Multiple compound release



# *Clinical trial*

- Chips are communicated with over a special frequency called the Medical Implant Communications Service Band, approved by both the FCC and the FDA.
- A patient or doctor enters a special computer code to administer or change the dose.
- Bidirectional communications link between the chip and receiver enables the upload of status information, including confirmation of dose delivery, battery life, etc.

# *Clinical trial*

- 8 patients
- PTH (compliance with injections is 25%)
- Small office procedure to implant
- Some pharmacokinetics (less variability) and Ca, PINP, CTX measures as daily injections

